

# **DIAGNOSIS**

**A Symptom-based Approach in Internal Medicine**



**CS Madgaonkar**

**JAYPEE**

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in Internal Medicine**



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## **A Symptom-based Approach in Internal Medicine**

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**Diagnosis: A Symptom-based Approach in Internal Medicine**

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**Dedicated to**

*The memory of my dear brothers  
Ramakant and Vasant*



# PREFACE

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*The best physician is the one who is able to differentiate the possible and the impossible.*

Herophilus of Alexandria

*Diagnosis: A Symptom-based Approach in Internal Medicine* was conceived during my practice in general internal medicine. I wrote this book because I wished it had been written for me. Although there are many textbooks and excellent manuals devoted to symptom-oriented diagnosis, I personally felt the need for a book that provides the essential information necessary in a concise and practical method, and thus relieve one from time and labor in searching through voluminous medical textbooks on the diagnostic process of symptoms presented by patients in today's arduous ambulatory health care delivery system.

A *symptom* is commonly defined as, "Any affection which accompanies disease; a perceptible change in the body or its functions, which indicates disease, or the kind or phases of disease". The importance of symptoms, therefore, cannot be overemphasized because symptoms are why patients visit physicians; and based on their analysis, a physician attempts to make as accurate a clinical diagnosis as possible.

Many symptoms encountered in everyday practice may suggest undifferentiated problems and many may suggest problems that are self-limited, while many symptoms are characteristic of early disease. New or serious symptoms often drive patients to overcrowded office or emergency departments. However, physicians need medical resource that can deliver timely and effective diagnostic information which, besides providing diagnosis on an established or common disease, does not ignore other possibilities. Besides, relevant diagnostic investigations and clinical aspects of related disorders are essential to support the diagnosis of any disease and treatment accordingly. Thus, in a busy ambulatory care, diagnosis has to be made without it being unrecognized until advance disease is present, treatment options are limited, and prognosis may be unfavorable.

It is in this context, I have made an attempt to first project common symptoms encountered in internal medicine, especially as applicable to the epidemiological incidence to the adult patient population, and then create a framework in which a physician can arrive at a tentative diagnosis. The main features which remain constant for each symptom are:

- *Synopsis*: A symptom introduction in brief;
- *Differential diagnosis of the symptom*: Classified in three main groups, namely — common, occasional and rare;
- *Investigations*: In two sections, namely — general and specific;
- *Clinical notes*: In short paragraphs, helpful in the diagnosis of most of the diseases;
- *Red flags*: Key points highlighted to alert serious disorders not to be missed;
- *Tables*: To simplify and comprehensively illustrate text, wherever needed;
- *Selective glossary*: Brief summary of assorted, common and uncommon diseases, denoted by the sign "vide infra ↓↓"; and
- *References*: From various journals, textbooks, etc. where applicable.



Thus, the contents of this book are focused on commonly encountered symptoms, with their differential diagnosis in a concise form, which will lead to a working diagnosis and investigations. The emphasis is on the axiom, 'common diseases present commonly, and its converse, uncommon diseases present uncommonly'. However, pointers to 'red flags', i.e. uncommon manifestations of common diseases should alert the physician of serious diseases not to be missed. No attempt has been made to discuss etiology or pathology of illness, or the complexities of practice management.

The frequency with which a disease is encountered by physician will depend upon its prevalence in the region from which their patients are drawn and also their specialty; therefore, regional variations in the incidence of diseases or methodology, or guidelines for investigations and diagnosis are not discussed, which can be accessed from other relevant sources.

The book assumes much basic knowledge and the information it contains must be supplemented by further reading. However, my endeavor has been to cover a spectrum of symptoms, with emphasis on practical features of diagnosis, based on recent evidence-based guidelines. The contents of the book are intended for medical students, internists, and house-officers during their daily office or hospital practice, and also to physicians to boost their diagnostic skills during busy practice day, and preparation for 'rounds' and clinical teaching. I also anticipate that physicians of other specialties will also value this book as an easy-to-use ready-reference guide beyond their everyday experience and in various practice settings.

There is no substitute for knowledge, and this book, I believe, will make symptom-based diagnostic process more accessible to many physicians, and if it prompts others to delve further and achieve sophistication in this clinical expertise, then this book has accomplished its purpose.

Finally, I would welcome feedback, which can be posted to me via my website: [www.drasm.com](http://www.drasm.com), or email: [vidya\\_csm@yahoo.com](mailto:vidya_csm@yahoo.com), or to the publishers.

**CS Madgaonkar**

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## CHAPTER

# 1

# Abdominal Distension

## SYNOPSIS

Abdominal *distension*\* may be defined as an increase in the girth of the abdomen. It is noticed by the patient because of the increase in belt or clothing size, recent weight gain, or ankle edema. Its onset may be sudden or gradual, persistent or intermittent. It may be entirely asymptomatic. More often the patient may describe distension as *bloating*,<sup>1,2</sup> fullness, hardness, tightness or pressure. These symptoms are usually exacerbated by meals, fluctuate in intensity, and are worse in the day and settle overnight. Other symptoms such as belching, postprandial discomfort, nausea, vomiting, shortness of breath, localized pain, and constipation, if present, may provide clues for the etiology of abdominal distension. As a

\*The terms 'distension' and 'bloating' are largely used synonymously; however, it has been suggested that the term 'bloating' should be reserved exclusively for the subjective symptom of abdominal enlargement, with the term 'distension' being used only when there is an actual change in girth.

Bloating appears to be more frequently associated with visceral hypersensitivity, whereas distension is more often related to hyposensitivity and delayed transit. The two phenomena may not be precisely the same.

mnemonic device the causes can be remembered as five 'fs': fat (obesity), fluid (ascites), flatus (gastrointestinal), fetus (pregnancy), and feces (constipation). However, abdominal distension/bloating may be contributed to by several simultaneous conditions, and the diagnosis may be particularly challenging, especially in a subset of patients with *functional GI disorders* (FGIDs).<sup>3-6</sup> A careful history and physical examination are necessary to develop an adequate differential and investigations, including psychosocial evaluation, that will help in the cost-effective approach to the diagnosis and care of these patients, who are otherwise susceptible to receiving unnecessary, costly, and sometimes risky studies and treatments.<sup>7</sup>

## DIFFERENTIAL DIAGNOSIS

### Common

- FGIDs (*vide infra* ↓↓): (aerophagia; IBS, globus; rumination syndrome: *vide infra* ↓↓; dysmotility-like dyspepsia; gallbladder dysfunction; proctalgia fugax: *vide infra* ↓↓)
- Infestations diarrhea (giardiasis)
- Obesity (metabolic syndrome)

- Pregnancy
- Distended bladder
- Ascites
- Intra-abdominal lump (organomegaly, tumor, cyst, neoplasm).

## OCCASIONAL

- Peritonitis (bacterial, tubercular, perforated viscus)
- Intestinal obstruction (strangulated hernia, adhesions, fecal impaction)
- Paralytic ileus (intra-abdominal inflammation, metabolic, drug induced).

## RARE

- Ascites (constrictive pericarditis, portal hypertension, Meigs syndrome: *vide infra* ↓↓).
- Peritonitis (spontaneous bacterial peritonitis, i.e. SBP: *vide infra* ↓↓, malignancy)
- Toxic megacolon (pseudomembranous colitis, ulcerative colitis)
- Pneumoperitoneum (traumatic rupture or perforation of viscus)
- Malabsorption syndromes (secondary lactase deficiency)
- Hypoalbuminemia (malnutrition, liver failure).

## INVESTIGATIONS—GENERAL

### CBC

- Leukocytosis in bacterial infection, inflammation (e.g. infections diarrhea, peritonitis); eosinophilia in parasitic infection
- Microcytic or megaloblastic anemia in malabsorption syndrome.

### ESR

- Elevated in infection, inflammation and malignancy.

### Urinalysis

- Albuminuria in renal disorders
- Urobilinogenuria may be present in hepatic disorders, absent in complete biliary obstruction
- In women, hCG to rule out pregnancy.

### Stools

- Ova, cysts, and parasites; rule out giardiasis
- Occult blood in carcinoma
- Steatorrhea in malabsorption syndromes.

### LFTs

- Bilirubin (mostly conjugated) often elevated
- Aminotransferases like ALT (i.e. SGPT), AST (i.e. SGOT) markedly elevated in cirrhosis of the liver
- Alkaline phosphatase (ALP) elevated in any biliary obstruction.

### AXR

- Dilated loops of intestine with multiple air-fluid levels in intestinal obstruction.

### US Abdomen/Pelvis

- Can confirm the presence of ascites suspected at physical examination
- Can detect as little as few milliliters of fluid located in obscure area, such as subdiaphragmatic region
- Can help determine the cause of ascites such as cirrhosis, portal hypertension, portal and hepatic vein thrombosis
- Can guide paracentesis; particularly useful in the presence of small amount of ascitic fluid or when the fluid is compartmentalized

- To assess organomegaly, hepatobiliary obstruction, and presence of a mass
- In women—to evaluate pregnancy, uterine, or ovarian lesion.

## INVESTIGATIONS—SPECIFIC

### Tuberculin or PPD and Casino's Test

- In TB and hydatid cyst.

### Serum Lipase

- May be elevated with pancreatic carcinoma, pancreatitis or perforated viscus.

### CT/MRI Scan

- Often has a complimentary role with US in the evaluation of patients with ascites, especially in patients with obscure source of ascites
- Can evaluate and confirm intra-abdominal or retroperitoneal mass lesion
- Valuable in the diagnosis of acute distension of abdomen suspected to be due to trauma, ruptured viscus, hemorrhage, obstruction, bowel ischemia, or leaking abdominal aneurysm.

### MRI Angiography

- In patients with hepatic or portal vein thrombosis or obstruction by tumor.

### Diagnostic Paracentesis

- Ascitic fluid analysis for Gram's stain, AFB, culture and cytology
- Estimation of amylase, lipase, and triglycerides to rule out pancreatitis and chylous ascites
- Recent statistical data indicate that the exudate-transudate concept should be discarded in the classification of ascites

because the estimation of the *serum ascites albumin gradient* (SAAG: Table 1.1) and ascitic fluid cholesterol is found to be a better marker in the diagnosis of ascites due to:

- Portal hypertension (a high gradient > 1.1 g/dl indicates that the ascites is due to portal hypertension; and a low gradient <1.1 g/dl indicates ascites of nonportal hypertensive etiology)<sup>8,9</sup>
- To distinguish malignant from non-malignant causes of ascites.<sup>10</sup>

**Table 1.1:** Causes of ascites by the serum ascites albumin gradient (SAAG)

#### High gradient (>1.1 g/dl)

- Cirrhosis\*
- Alcoholic hepatitis
- Fulminant hepatic failure
- Massive liver metastasis
- Congestive cardiac failure, constrictive pericarditis (cardiac ascites)
- Myxoedema, Budd-Chiari syndrome (hepatic vein thrombosis), or Veno-occlusive disease.

#### Low gradient (<1.1 g/dl)

- Peritoneal tuberculosis
- Nephrotic syndrome
- Peritoneal carcinomatosis
- Pancreatic ascites
- Biliary ascites
- Bowel obstruction/infarction

\*Patients with high SAAG most often have portal hypertension.

### Laparoscopy with Biopsy

- Direct visualization of abdominal and pelvic organs to detect extra-abdominal mass, peritoneal deposits of tumor, TB, or metastatic disease of the liver. Biopsies are taken under direct vision to enhance diagnostic accuracy.

### Exploratory Laparotomy

- In undetermined etiology with adequate investigations.



## CLINICAL NOTES

- Acute abdominal distension may signal life-threatening peritonitis or acute intestinal obstruction. A rapid check for signs of hypovolemia, such as pallor, thready pulse, diaphoresis, hypotension, altered mentation and focussed physical examination is indicated for urgent diagnosis and management
- While dealing with patients with FGIDs, developing an effective patient-physician relationship through empathy, reassurance, and education is most rewarding
- History—Includes onset, duration; weight gain ( $\text{BMI} > 30 \text{ kg/m}^2$ ); weight loss (tubercular abdomen, diabetic gastroparesis, anorexia nervosa, malignancy); bowel movements—constipation, diarrhea or altered bowel habits (IBS, malignancy); diet (excess fiber, milk or its products); medications (diphenoxylate, cisapride); substance use or abuse (laxatives, ecstasy); personal/social stress factors (food habits, smoking, alcohol); and family history (diverticulosis, polyposis)
- Physical examination—Febrile episodes; abdominal tenderness, dilated veins, bowel sounds or mass; inguinal and femoral hernia; measuring the abdominal girth for a baseline value; and pelvic examination in women are important
- Physical tests for ascites such as flank dullness, shifting dullness, and the *puddle* sign are not helpful when a small volume (less than 1 liter) of ascites exists
- Ascites is rarely the sole physical finding. Once identified, investigations should follow to determine its cause
- Development of symptoms of fever, abdominal pain, or mental status changes (encephalopathy) in a patient with ascites indicates complication such as SBP which has poor prognosis
- *Mixed ascites*, i.e. ascites from two different causes may coexist in few patients with ascites, e.g. cirrhosis of the liver with CHF/pancreatitis/tuberculosis/malignancy.

## RED FLAGS

- Aerophagia is not always ‘neurotic’; swallowing air may be a response to abdominal discomfort from organic disease
- Patients with FGIDs with psychological difficulties such as depression, panic, somatization, and personality disorders may need psychologist or psychiatric referral
- Swallowed air (aerophagia) that is not eructed may get trapped in the splenic flexure (colon makes a 90 degree turn at this location) causing distension with gas of that part of the large intestine in the region of the spleen. Since this location is just beneath the diaphragm, the location of the pain appears to be coming from the lower left chest, causing discomfort or pain which may be referred to left side of chest, shoulder or arm. This *splenic flexure syndrome* (SFS) may be mistaken for a coronary event. However, it may be distinguished from cardiac pain by its intermittent, colicky behavior and fluctuations in intensity of the pain. Also relief of pain of SFS is characteristically obtained by defecation.

## SELECTIVE GLOSSARY

### Functional GI Disorders (FGIDs)<sup>7, 11, 12</sup>

*FGIDs* is defined as a variable combination of chronic or recurrent GI symptoms not explained by structural or biochemical abnormalities. It cannot be diagnosed through endoscopic, radiologic, or laboratory studies. Furthermore, even though these disorders share certain physiologic characteristics (such as abnormal

motility and visceral hypersensitivity) that are associated with symptom generation, the findings are not specific for diagnosis, and the clinician has limited ability to evaluate them in practice. In the absence of any objective marker, the identification and classification of FGIDs are based on symptoms, and consist of a wide spectrum of syndromes which cross over and in some cases overlap various anatomic areas of the luminal gut. Although IBS has traditionally been the most studied and written about, FGIDs constitute a number of unique disorders, including functional esophageal disorders (noncardiac chest pain, functional dysphagia, and globus sensation); functional dyspepsia (pain, discomfort, nausea, and other symptoms above the navel in persons who do not meet the diagnostic criteria for IBS); functional abdominal pain syndrome; functional abdominal bloating; functional diarrhea; functional disorders of the biliary tract, including Oddi sphincter; functional disorders of the anorectal area, such as pelvic floor dyssynergia; and proctalgia fugax. The diagnosis of FGIDs relies heavily on the clinical history, a limited diagnostic evaluation and early symptomatic treatment that include symptom monitoring and reassessment. There is increasing evidence that psychopharmacologic and psychotherapeutic management of FGIDs are highly effective and, in many instances, surpass the efficacy of standard medical treatment.

### **Meigs Syndrome**

Meigs syndrome is defined as the triad of benign ovarian tumor with ascites and pleural effusion that resolves after resection of the tumor. The ovarian tumor in Meigs syndrome is a fibroma. Pseudo-Meigs syndrome consists of pleural effusion, ascites, and benign tumors of the ovary other than fibromas. Pseudo-pseudo Meigs syndrome includes patients with

systemic lupus erythematosus and enlarged ovaries.

### **Proctalgia Fugax**

Proctalgia fugax is a diagnosis of exclusion, and defined as sudden, severe pain in the anorectal region lasting several seconds or minutes, and then disappearing completely. It is common but largely underreported. The etiology is not well-defined. Attacks are infrequent, left-sided, and short-lived. Patients are asymptomatic between episodes. The discomfort is usually triggered by stressful event; can occur during the day or night; although it is not typically associated with bowel movements, it may be relieved by heat, anal dilatation, or relaxation techniques.

### **Rumination Syndrome**

Rumination means repeated regurgitation (backflow of food from the stomach into the mouth) and rechewing of food, i.e. voluntary or involuntary regurgitation and rechewing of partially digested food that is either re swallowed or expelled. This regurgitation appears effortless, may be preceded by a belching sensation, and typically does not involve retching or nausea. In rumination, the regurgitant does not taste sour or bitter. The behavior must exist for at least 1 month, with evidence of normal functioning prior to onset. Rumination occurs within a few minutes postprandial and may last 1-2 hours. Though frequency may vary, rumination typically occurs daily and may persist for many months or years. Although the etiology of rumination is unknown, multiple theories have been advanced to explain the disorder. These theories range from psychosocial factors to organic origins. Cultural, socioeconomic, organic, and psychodynamic factors have been implicated.



### Spontaneous Bacterial Peritonitis (SBP)

SBP is a bacterial infection of ascitic fluid in patients with decompensated cirrhosis. The term '*spontaneous*' distinguishes this from surgical peritonitis. Enteric organisms are isolated from more than 90% of infected ascites fluid in SBP, suggesting that the GI tract is the source of bacterial contamination. Symptoms of infection occur in most patients with SBP, including fever, abdominal pain, mental status changes, and ileus. A high index of suspicion should exist for SBP in patients with cirrhosis and ascites, especially in those who do not improve following administration of diuretic medication.

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## CHAPTER

# 2

## Abdominal Pain

### SYNOPSIS

*Abdominal pain* is a subjective sensation of a noxious internal stimulus. Classic teaching separates abdominal pain into three categories based on underlying pathophysiology, namely visceral, parietal, and referred.

*Visceral* pain (originating via autonomic fibers within the organ itself, hence the name *visceral*, referring to viscera organs) occurs when the solid or hollow viscous organs such as kidney, liver, spleen, bowel, gallbladder, and urinary bladder are involved. Most organs do not have many nerve endings (mediated primarily by bilateral unmyelinated afferent C fibers which are slow transmitters), so the pain is generally slow in onset; may be mild, diffuse, and poorly localized, meaning the patient will have difficulty pointing to the pain with one finger. Most often the patient will wave his or her hand over the area indicating a general or more diffuse pain; usually described as dull, aching, or crampy, may be intermittent or constant. It arises from distension or spasm of a hollow organ, e.g. the discomfort experienced early in intestinal obstruction, or inflammation in cholecystitis. Less commonly it is caused by

early ischemia or by direct involvement of sensory nerves, e.g. malignant infiltration. Visceral pain is most often felt in the midline because of the bilateral sensory supply to the spinal cord, and produce associated nausea, vomiting, diaphoresis and tachycardia.

*Parietal* pain, also referred as *somatic* pain, usually signifies peritoneal lining irritation by blood, fluid or other organ contents. Peritoneum has a larger number of highly sensitive nerve endings (mediated by fast transmitting both myelinated afferent C, and A delta nerve fibers), so pain is more acute, better localized—the patient will typically be able to point to the pain with one finger—and more intense, usually described as sharp and constant. The pain is localized to the dermatome above the site of stimulus. Initially, parietal pain is perceived as unilateral because the parietal peritoneum is innervated only from one side of the nervous system. Patients with peritoneal irritation usually lie very still with the legs drawn up towards the chest in what appears to be a fetal position, which helps to relax the parietal peritoneum and thus reduces pain. Also, the patient will breathe shallow and fast to reduce

movement of the diaphragm and subsequent aggravation of the peritoneum. When visceral pain is replaced by parietal pain, it is typically an indication that the condition has progressed, and is potentially worsening, e.g. the pain of acute appendicitis—felt initially around the umbilicus as visceral pain, and then becomes localized to the right iliac fossa as parietal or somatic pain when the peritoneum becomes involved.

*Referred* pain is a type of visceral or organ pain that is felt away from the actual affected organ site, even though the patient is complaining of discomfort or pain in that particular area. Because of fewer nerve endings in the organs, the brain may misinterpret (i.e. cortical misperception of either visceral or parietal afferent stimuli; viscerosomatic convergence) where the pain is coming from. For example, cholecystitis pain is commonly referred to the right shoulder area; renal pain is commonly felt in the testis on the same side; and appendicitis may also manifest by pain in the right testis.

Patterns of referred pain are also based on embryologic sharing of dermatomes. (Table 2.1). A pair of sites may share development from the same embryologic tissue, and may share innervation to some extent. Therefore, pain at one site may be referred to the other site, even though the pathologic site is not painful initially. For example, epigastric pain may be the initial symptom of appendicitis; acute cholecystitis may cause shoulder pain; acute inferior wall myocardial infarction may cause abdominal pain. Just as abdominal conditions may cause referred pain outside of the abdominal cavity, the same is true for some extraintestinal and abdominal conditions (Table 2.2).

Although each type of pain is thought to have a different neuropathophysiology, the categories are not entirely discrete because of variability in innervation between patients, and due to the complex dual visceral and parietal sensory

**Table 2.1:** Embryogenic location of abdominal pain

Origin	Organs levels	Spinal locations	Pain
Foregut	Distal esophagus, stomach, proximal (first two parts) duodenum, liver, biliary tree, pancreas	T5-T6 to T8-T9	Between xiphoid and umbilicus, i.e. epigastrium
Midgut	Duodenum (3rd and 4th parts) Small intestine, appendix, ascending colon, proximal 2/3 of transverse colon	T8-T11 to L1	Periumbilical
Hindgut	Distal 1/3 of transverse colon, descending colon, rectosigmoid Reproductive organs (ovaries, fallopian tubes, uterus, seminal vesicles, prostate), bladder	T11- L1	Between umbilicus and pubis, i.e. suprapubic

**Table 2.2:** Extraintestinal and extra-abdominal causes of acute abdominal pain: what not to miss

Diagnosis	Investigations/remarks
<b>Cardiac:</b> Acute MI; especially inferior wall	Usually elderly patient; cardiac risk factors present; obtain ECG/cardiac enzymes
<b>Vascular:</b> Ruptured abdominal aneurysm Mesenteric infarction	Request abdominal US; HRCT/MRI Abdominal duplex US; MR mesenteric angiography
<b>Pulmonary:</b> Pulmonary embolism; lower pneumonia	Subdiaphragmatic referred pain; CXR; HRCT
<b>Metabolic:</b> Diabetic ketoacidosis; Hypercalcemia (hyperthyroidism or malignancy)	Blood glucose; ketones; electrolytes; ABG 'Stones, bones, abdominal moans, and psychic groans'; serum calcium; PTH
<b>Hematological:</b> Porphyria-acute intermittent Sickle-cell disease	Typical urine discoloration; urine porphobilinogen Hemolytic anemia; sickled erythrocytes; hemoglobin electrophoresis
<b>Gynecological:</b> Ectopic pregnancy-ruptured	Missed if pregnancy is not confirmed in women of child-bearing age

Contd...

Contd...

<b>Abdomen:</b> Pancreatitis; pancreatic carcinoma	History of alcohol abuse; hyperlipidemia; serum lipase; US abdomen or CT scan
<b>Spine:</b> Vertebral compression; herpes-zoster	Pain in relation to nerve root involvement
<b>Psychogenic:</b> Somatization disorders; FGID	Bizarre signs and symptoms; repeated negative work-up

network innervating the abdominal area, e.g. visceral pain often blends with parietal pain as a pathologic process evolves. The parietal pleura may be involved in cases of pneumonia and the pain is predominantly felt in the central abdomen. The pain of myocardial infarction may also be felt predominantly in the central abdomen instead of in the precordial region. Further, classical descriptions of abdominal pain have limitations because individuals react to pain differently. An elderly or a diabetic may not be much aware of abdominal pain or discomfort due to mesenteric ischemia. Moreover, abdominal pain is often a nonspecific complaint that presents with other organ disorders, e.g. severe headache in a patient with abdominal migraine, altered sensorium in a patient with diabetic ketoacidosis, weight loss in anorexia nervosa, and neoplastic disease. Thus, the overall sensitivity and specificity of the history and physical examination in diagnosing the different causes of abdominal pain is poor, particularly for benign conditions.<sup>1,2</sup>

The causes of abdominal pain are legion, embracing all age groups and specialties (Table 2.3). The spectrum of diseases ranges from life-threatening to benign. Often the diagnosis cannot be established in a single encounter. Though newer imaging modalities have succeeded in solving many challenging problems, an odd case continues to be a daunting task—being extremely difficult to pinpoint its source of distress—a situation often metaphorized as *Pandora's Box*. Therefore, it's probably more important to first exclude life-

threatening etiologies of *acute abdomen*\* such as a dissecting aneurysm, perforation, or obstruction, than to make a specific diagnosis. Once these have been reasonably excluded, a systematic approach should be employed to obtain a thorough history and physical examination with pertinent laboratory, radiologic, and endoscopic procedures. The choice of the most appropriate test is determined by a host of factors; however, any shotgun approach to abdominal pain, although tempting and frequently reassuring, should be avoided.

**Table 2.3:** Common causes of acute abdominal pain in hospitalized patients

#### *All age groups*

- NSAP
- Appendicitis
- Renal colic
- Acute urinary retention
- Acute cholecystitis
- Acute pancreatitis
- Perforated peptic ulcer
- Intestinal obstruction
- Diverticular disease

#### *Elderly*

- Medical causes (MI, pneumonia, DKA)
- Vascular (MI, mesenteric ischemia, AAA)
- Cancer (colorectal)

#### *Children*

- Upper respiratory tract infection
- Urinary tract infection
- Hernia
- Intussusception

#### *Women—obstetric*

- Ectopic pregnancy
- Abortion problems (septic abortion)
- Acute hydramnios
- Concealed accidental hemorrhage
- Perforating mole
- Rupture uterus
- Imminent eclampsia

#### *Women—gynecologic*

- Misplaced IUCD
- Fibroid
- Ovarian tumor (Torsion)

\*The term *acute abdomen* is defined as severe abdominal pain of *unclear etiology* lasting for several hours, which might indicate a progressive intra-abdominal condition that is threatening to life or capable of causing severe morbidity; hospital admission is usually necessary and operative surgery is the most likely outcome. However, not all patients turn out to have such a threatening condition but they need to be considered as being in danger until surgical evaluation has been completed.

## DIFFERENTIAL DIAGNOSIS

### Common

- Nonspecific abdominal pain (NSAP<sup>†</sup> Table 2.4).

**Table 2.4 : Nonspecific abdominal pain (NSAP)**

- **Clinical presentation and causes**
  - Viral infections: Mesenteric adenitis
  - Bacterial infection: Acute bacterial gastroenteritis
  - Worm infestation: Roundworm, hookworm, threadworm
  - Parasitic infestation: Amebiasis, giardiasis
  - Abdominal wall pain: Hematoma, hernia, herpes zoster, nerve entrapment, 'rib-tip' syndrome
  - Functional: IBS
  - Gynecological: PID, Mittelschmerz pain (*vide infra* ↓↓), ovarian cyst
  - Others: Food allergy, abdominal epilepsy, abdominal migraine, myofascial pain syndrome (*vide infra* ↓↓), spinal referred pain
  - Psychogenic: Conversion disorder

- Systemic disease (gastroenteritis, viral hepatitis A, UTI)
- Appendicitis
- Peptic ulcer disease (PUD)
- Biliary colic (cholecystitis, cholelithiasis)
- Renal colic (calculus)
- Gynecological (dysmenorrhea, PID).

### Occasional

- Abdominal wall pain (postoperative scars, herpes zoster, abdominal hernia, trauma)
- Intraperitoneal lesion (infections—abscess, tuberculosis, pancreatitis; mass lesion)
- Perforation (appendix, typhoid ulcer, duodenal ulcer)
- Obstruction (intestinal, volvulus, strangulated hernia, ileus)
- Internal hemorrhage (ruptured ectopic pregnancy/ovarian cyst/Graafian follicle)
- Torsion (ovarian cyst, pedunculated fibroid, testis).

<sup>†</sup>NSAP is defined as an acute, self-limiting pain of short duration and indeterminate cause, which requires no surgical treatment.

### Rare

- Cardiorespiratory (MI, aortic dissection, pneumonia)
- Malignancy (gastric, pancreatic, metastasis)
- Metabolic (DKA, uremia, hypercalcemia, Addison's disease)
- Hematologic (hemolytic crisis, porphyria)
- Ischemic (mesenteric thrombosis, i.e. abdominal angina)
- Allergy (lactose intolerance, gluten sensitivity)
- Psychogenic (Munchausen's syndrome – *vide infra* ↓↓, somatization disorder).

## INVESTIGATIONS—GENERAL

### CBC

- Anemia with chronic blood loss, e.g. PUD, malignancy
- Chronic hemolytic anemia and abnormal RBCs in peripheral blood smear in sickle cell disease
- Leukocytosis may be seen in infective process; however, a normal WBC count does not exclude a serious cause of abdominal pain.

### ESR

- Elevated with infection, malignancy.

### Urinalysis

- Hematuria in infection, calculi, malignancy; pus cells in infection
- Increased urobilinogen in viral hepatitis, absent in complete biliary obstruction
- Ketones in DKA
- Porphobilinogen in porphyria.

### Fecal Occult Blood

- May be positive in PUD, mesenteric ischemia, carcinoma of colon, Crohn's disease, and diverticulitis.

### Blood Glucose

- To monitor glycemic control in diabetes complicated by DKA.

### LFTs, Amylase, Lipase

- ALT and AST markedly elevated in acute hepatitis
- Sustained elevation of serum alkaline phosphatase and presence of HBsAg or anti-HCV in hepatocellular carcinoma may be seen
- Serum amylase and lipase elevated significantly (three times normal) in acute pancreatitis, perforated ulcer, and mesenteric thrombosis.

### Urea, Creatinine, Electrolytes

- To assess the state of hydration, and to rule out renal disease.

### ECG

- To rule out MI, atrial fibrillation.

### Pregnancy Test

- Indicated in all women of childbearing age to exclude normal (before imaging procedures) or ectopic pregnancy.

### US Abdomen

- Preferred in pregnant women to minimize radiation
- In general right upper quadrant pain is best evaluated initially by US, such as due to hepatobiliary diseases
- It is also helpful in evaluating appendicitis, gynecological disease, intra-abdominal fluid, abscesses, and pregnancy—both normal and ectopic
- Transvaginal Doppler US may be indicated to further confirm or exclude ectopic pregnancy
- Although US remains the primary modality by which complaints specific to the pelvic pain in women are evaluated, in many instances, CT and MRI imaging, due to their improved technology have become equal to that of ultrasound in diagnosing causes of pelvic pain in women.<sup>3,4</sup>

## INVESTIGATIONS—SPECIFIC

### HRCT Scan

- In general, nonenhanced HRCT scanning of the entire abdomen and pelvis is proved to be the single most accurate factor for identifying need for urgent intervention in patients with acute nontraumatic abdominal pain, including those associated with retroperitoneal structures. Many inflammatory, ischemic, and mass lesions such as appendicitis, cholecystitis, diverticulitis, hernia, obstructed or perforated bowel, pancreatitis, renal colic, and acute bowel ischemia can be evaluated with high degree (>90%) of sensitivity and specificity
- A contrast enhanced CT scan is invaluable in the work-up of patients with hepatic, pancreatic, and renal disorders
- HRCT can be considered a better alternative than IVU because it has a higher diagnostic accuracy, faster, less expensive and less risky than IVU. In addition, it also has the capability of detecting various additional renal and extrarenal pathologies<sup>5</sup>
- CT scan is also helpful to guide biopsies and other minimally invasive procedures.

### MRI

- Provides diagnostic information in the work up of patients with hepatic, adrenal, pancreatic disease, and lesions associated with mesenteric circulation.

### Endoscopy

- EGD may be indicated in the diagnosis of upper GI bleeding (PUD, esophageal varices)
- Sigmoidoscopy or colonoscopy for rectal, sigmoidal, or colonic obstruction
- Cystoscopy for lower renal disease.



### CXR—Upright View

- In patients with visceral perforation, free intraperitoneal air can be seen as a crescent of lucency under the right diaphragm (as this is at a higher level). The amount of air as little as 1 to 2 ml is detectable
- Parenchymal consolidation, CHF, or pleural lesion that may be the cause of referred pain to the abdomen can also be confirmed
- Those who cannot maintain upright position, lateral decubitus view, and across the table view may be helpful. In lateral decubitus view, free air can be viewed between the right edge of the liver and the lateral right diaphragm. In across the table view, air may be viewed just behind the parities
- US of abdomen is shown to be superior to the erect CXR for the detection of free intraperitoneal gas.<sup>6,7</sup>

### AXR

- Supine plus erect or decubitus views to primarily evaluate GI gas pattern, i.e. air under diaphragm or multiple air-fluid levels, indicative of perforated ulcer or viscus, or bowel obstruction<sup>#</sup>
- Other lesions such as renal calculi; gallstones, gas in biliary tree in gallstone ileus; aortic calcification (aneurysm); and obliteration of

psoas shadows (retroperitoneal inflammation or hemorrhage) may be seen.

### Magnetic Resonance Cholangiopancreatography (MRCP)

- This has largely replaced the invasive diagnostic ERCP in delineating the cause of obstructive jaundice.

### Endoscopic Ultrasound (EUS)

- This is a recent innovation in the world of endoscopy. Its advantage over conventional endoscopy is its ability to provide transmural details. Also, it is extremely useful in small tumors that cannot be properly assessed by CT scan. The option of EUS-guided fine needle aspiration cytology (FNAC) and brush cytology is an added asset in selected situations.

### Radionuclide Scans

- Liver-spleen scans, HIDA scans, and gallium scans may be useful in localizing intra-abdominal abscesses (now replaced by CT scans)
- <sup>51</sup>Cr-labelled erythrocyte scans may be useful to identify the source of intermittent or slow GI bleeding
- <sup>99m</sup>TcTechnetium pertechnetate scans are helpful in the diagnosis of Meckel's diverticulum.

### Angiography

- Percutaneous invasive angiography or magnetic resonance angiography (MRA) is indicated if intra-abdominal intestinal ischemia or ongoing hemorrhage is suspected. Selective visceral angiography is a reliable method of diagnosing mesenteric infarction.

### Other Imaging

- Upper GI barium series or enema with double contrast media, and IVP are rarely

<sup>#</sup>Numerous signs are described for pneumoperitoneum on plain radiographs. The *Rigler sign*, or the double-wall or bas-relief sign, is a visualization of the outer surface of a bowel loop wall as a result of free air in the peritoneal cavity. The intraluminal gas provides negative contrast and outlines the internal wall. The *cupola sign*, typically seen on supine radiographs, is an inverted cup-shaped arcuate lucency overlying the lower thoracic spine and projecting caudally to the heart. This sign is formed as air accumulates anteriorly in the median subphrenic space under the central leaf of the diaphragm. The *football sign*, typically seen in pediatric patients, is a visualization of the entire peritoneal cavity as an oval gas shadow, with the vertically oriented falciform ligament representing the seam of an American football.

indicated (time consuming and excess radiation exposure). However, where CT scan facility is lacking, a barium enema will confirm the diagnosis of volvulus of sigmoid colon ('beaked' appearance). IVP may be needed occasionally when it is difficult to differentiate right sided ureteric colic and acute appendicitis. In such cases a single film IVP is found to be useful. In ureteric colic there may not be secretion of dye on the affected side, or there may be hold up in the line of ureter. Intravenous cholangiography is now replaced by US and HIDA scans in the diagnosis of jaundiced patients and those suspected with cholangitis.

### FNAC and Biopsy

- Histopathological or exfoliative cytology of superficial lesion, e.g. in patients suspected with lymph node tuberculosis, or metastasis; or ultrasound/CT guided biopsies of abdominal organs; or endoscopically obtained specimen in inflammatory or malignant disease, e.g. abdominal TB, hepatocellular carcinoma, metastatic liver disease, adenocarcinomas, lymphomas, and neoplastic lesions of retroperitoneal organs like kidneys and adrenals.

### Paracentesis

- In patients with SBP, TB peritonitis, chylous ascites, and for peritoneal cytology.

### Laparoscopy

- A less invasive procedure for the diagnosis of extraluminal, intra-abdominal solid lesions which cannot be visualized by endoscopic procedures.

### Surgical Exploration

- May be required in a few complicated or undiagnosed cases, e.g. intestinal adhesions,

obstruction, perforation; acute biliary disease, ectopic pregnancy, etc. particularly if there is preoperative diagnostic uncertainty. Biopsy of the pathological organ may be performed.

## CLINICAL NOTES

- Perhaps in no other situation is the history and physical examination more important in arriving at a rapid diagnosis than in the acute abdomen.<sup>\$</sup> Decisions have to be made quickly with minimum investigations. Therapeutic efforts have to be instituted often within minutes. A structured data sheet\*\* is now widely used in many health services as *aide-memoire* to minimize diagnostic errors
- Special points to note in the general examination in a patient with an acute abdomen include: general appearance (well looking, or ill, thin, emaciated); alertness or state of consciousness; hydration; temperature-pulse-respiration; and blood pressure. Life-threatening causes (Table 2.5) should always be ruled out before focussing on less serious diagnosis. Periodic examination and critical assessment of the changes in the condition of the patient, including vital signs and appearance are clues to risk stratification and appropriate diagnosis
- A careful examination of hernial sites, scrotum, pelvis, and rectal examination is mandatory in every patient with abdominal pain—especially in acute cases to rule out intestinal obstruction.

<sup>\$</sup>Dr Zachary Cope in the classical text *Cope's Early Diagnosis of the acute Abdomen*, reminds us that, "the general rule can be laid down that the majority of severe abdominal pains that ensue in patients who have been previously fairly well, and that last for as long as six hours, are caused by conditions of surgical import".

\*\*For a typical example refer to—Michael M Henry et al. *Clinical Surgery*, 2nd International edn.; Publisher: WB Saunders Company; Chapter 22—Acute Abdominal Conditions—p. 367.



**Table 2.5:** Physical findings in various acute abdominal conditions

Condition	Helpful symptoms and signs
Hemorrhage (Internal)	Increasing restlessness; air-hunger; pallor; shock; increasing distension; pulsatile (aneurysm) or tender (ectopic pregnancy) mass; rectal bleeding (occasionally)
Obstruction (Intestinal)	Patient anxious, restless; vomiting (in high obstruction); constipation (in low obstruction); Distension; hyperperistalsis (early); visible peristalsis (late); 'silent abdomen' (late); diffuse pain without rebound tenderness
Torsion (sigmoid colon/ovary)	Sudden, severe pain; rapid distension; palpable sigmoid colon (like a pneumatic tyre) in left lower abdomen; or in a female palpable, freely mobile, cystic swelling in the lower abdomen
Vascular (ischemia)	Patient elderly; atherosclerosis or valvular heart disease; post-prandial acute pain but little tenderness; not distended (till late); rectal bleeding (occasionally)
Inflammation (mass or abscess)	Fever; Tender mass (abdominal, Rectal, or pelvic); special signs (Murphy's psoas, Obturator)
Peritonitis	Patient motionless; fever; tachycardia; cough and rebound tenderness; board-like rigidity (late); absent bowel sounds
Perforation (viscus)	Patient pale, anxious, lies still in bed; vomiting; rising pulse; hypotension; tenderness, rigidity (early); increasing distension; diffuse tenderness (late); loss of liver dullness; absent bowel sounds

Note: mnemonic "HOT – VIP (double) P"

- In a woman with abdominal pain a detailed gynecological history, including the timing of LMP, pregnancy history, and vaginal discharge or dysmenorrhea should be obtained
- Pregnant women with abdominal pain, in addition to all other causes of abdominal pain, may present with atypical locations of abdominal conditions.<sup>8,9</sup> Also, prior to examination of the abdomen, the patient should empty the bladder
- History of collapse or fainting in a patient with abdominal pain is suggestive of an acute vascular catastrophe such as internal hemorrhage, ruptured ectopic pregnancy, acute pancreatitis, torsion, strangulation, or mesenteric vascular thrombosis or embolism
- Past history of abdominal surgery makes intestinal obstruction from adhesions more likely
- In elderly patients with history of CAD or presence of cardiac risk factors with abdominal pain, especially upper abdominal pain of acute onset, obtain an ECG to rule out MI
- In elderly patients with abdominal pain associated with skin xanthomas and generalized atherosclerosis, the possibility of MI, AAA, and mesenteric ischemia must be excluded by obtaining ECG, US, or CT scan
- Drug history should include prescription and illicit drug use as well as alcohol. NSAIDs, steroids and immunosuppressants facilitate perforation or peritonitis. Anticoagulants enhance bleeding and hematoma formation. Alcohol predisposes to pancreatitis. Purgatives may ease perforation in a case of acute appendicitis. Sulpha, steroids, barbiturates, estrogen, beta-blockers are known to precipitate porphyria. Megadoses of vitamin A and D, diuretics, lithium, oral calcium intake lead to hypercalcemia which may present with acute abdominal pain
- There are specific signs associated with certain specific diagnosis (Table 2.6); these should be elicited where applicable.
- Biliary diseases such as cholecystitis, cholelithiasis occur commonly in a fatty, flatulent, fertile, and female of forty

**Table 2.6:** Significance of named signs in abdominal pain conditions

<i>Sign</i>	<i>Description</i>	<i>Significance</i>
Carnett's sign	Contract the abdominal musculature by raising the head or straightened legs off the table	To differentiate abdominal wall pain from intra-abdominal pain
Cullen sign	Periumbilical ecchymosis	Intraperitoneal hemorrhage (due to hemorrhagic pancreatitis, ruptured ectopic pregnancy); retroperitoneal hemorrhage
Turner sign	Bruising of flanks	Acute pancreatitis; ruptured AAA; severe abdominal injury
Rovsing sign	More RLQ pain with palpation of LLQ	Acute appendicitis
Obturator sign	RLQ pain with internal rotation of the fixed right hip	Acute appendicitis
Psoas sign	RLQ pain with hyperextension of the right hip	Acute appendicitis
Murphy sign	'Catch' in the breath on finger pressure in RUQ	Acute cholecystitis
McBurney's sign	Tenderness located 2/3 distance from anterior iliac spine to umbilicus on right side	Acute appendicitis
Kehr's sign	Severe left shoulder pain	Splenic rupture, Ectopic pregnancy rupture

## RED FLAGS

- Catastrophic abdominal emergencies such as perforated peptic ulcer or internal hemorrhage may be associated with minimal or no detectable pain or muscle spasm in frail elderly, seriously ill patients, and in patients with HIV infection, or those taking immunosuppressants. A thorough work up and admission is usually warranted
- Intrathoracic diseases that most often masquerade as abdominal emergencies (MI, PE, pneumonia, pericarditis, and esophageal disease) must be considered in every patient with abdominal pain, especially if the pain is in the upper part of the abdomen
- Whenever the cause of abdominal pain is obscure, a metabolic or vascular origin (diabetes mellitus, Addison's disease, mesenteric ischemia, and porphyria) must always be considered
- Beware of *silent abdomen*—the temporary improvement (easing of pain) in a patient with perforated appendix or peptic ulcer with peritonitis; it could be misleading
- Screen any women in the reproductive age with history of missed period and presenting with abdominal pain, vaginal bleeding, or spotting for pregnancy—normal or otherwise. An ectopic pregnancy can present even before a missed period
- In a patient with recurrent abdominal pain with repeated negative work up—rule out *three Ps*, i.e. pancreatitis, porphyria, and psychiatric disorder.

## SELECTIVE GLOSSARY

**Mittelschmerz pain** (pronounced mitel-schma-rt̩s). It is the ovulation pain or midcycle pain—pain associated with ovulation. The pain may occur just before, during, or after ovulation. Symptoms include lower-abdominal pain that is:

- One-sided
- Recurrent or with similar pain in past

- Typically lasting minutes to a few hours, but may extend as long as 24-48 hours
- Usually sharp, cramping, distinctive pain.
- Severe (rare)
- May switch sides from month to month or from one episode to another
- Begins midway through the menstrual cycle.

*Signs and tests:* A pelvic examination shows no abnormalities. Other diagnostic procedures (such as an US abdomen) may be performed to rule out other causes of ovarian pain if ovulatory pain is prolonged.

**Munchausen syndrome** (pronunciation: Munchau-zen) was named after the Baron Karl Friedrich Hieronymus Freiherr von Munchausen, who was a German cavalry officer and known as a tremendous liar. Patients with Munchausen syndrome go from physician to physician dramatically presenting very plausible symptoms and histories and receiving care, up to and including surgery. They fake physical signs of illness and abnormal laboratory findings. The person may:

- Claim that he or she has symptoms, when none exist.
- Produce false test results, such as by sticking a thermometer in hot water to mimic a fever or by putting bacteria or something else in laboratory test samples.
- Self-inflict injuries, such as cutting the skin.
- Create symptoms, such as causing vomiting by taking medication.
- Say that symptoms are worse than they really are, such as claiming to have severe pain or bleeding when a milder condition is actually present.
- Request surgical procedures.

Approximately 50% of those with Munchausen syndrome are subject to drug abuse, and many have borderline personality disorder. The disorder generally starts during early adulthood, but may begin during childhood.

**Myofascial pain syndrome (MPS)**— Myofascial pain is a chronic, painful condition that affects the fascia, i.e. the connective tissue that covers the muscles-either a single muscle or a muscle group. Myofascial pain symptoms usually involve muscle pain with specific “trigger” or “tender” points. Trigger points can be identified by pain that results when pressure is applied to an area of the patient’s body. The pain can be made worse with activity or stress. In addition to the local or regional pain associated with MPS, people with this disorder also can suffer from depression, fatigue, and behavioral disturbances. No specific lab tests confirm the diagnosis of MPS, but lab tests can be helpful in looking for predisposing conditions, such as hypothyroidism, hypoglycemia, and vitamin deficiencies. Chronic infections and sleep deprivation have been cited as causative factors, as have radiculopathy, visceral diseases, and depression. The pathogenesis likely has a central mechanism with peripheral clinical manifestations.

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## CHAPTER

# 3

## Amenorrhea

### SYNOPSIS

Normal menstruation depends on the integrated hypothalamic-pituitary-ovarian (HPO) axis and endometrial function, and a patent lower genital outflow tract. Briefly, the pulsatile hypothalamic gonadotropin releasing hormone (GnRH) stimulates release of pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate ovarian production of estrogen (17- $\beta$  estradiol) and progesterone. Sequential endometrial stimulation by estrogen initially, followed by progesterone, cause uterine endometrial proliferation (in preparation for possible nidation of fertilized ovum). Cyclical withdrawal of these hormones (in the absence of nidation) results in sloughing of the endometrium and menstrual bleeding.

In normal healthy women, the cyclical menstruation is mostly constant with an average rhythm of  $28 \pm 7$  days, inclusive of 4 to 6 days of bleeding which persists throughout the reproductive period of life.

*Amenorrhea* indicates the absence of menstruation; its onset may be primary or secondary. *Primary amenorrhea* is arbitrarily defined as failure of onset of menstruation beyond the age of 16 years regardless of development of secondary

sexual characteristics.\* *Secondary amenorrhea* refers to absence of menstruation for 3 consecutive months in women who have previously menstruated.<sup>@,1</sup>

Amenorrhea may be *physiological* such as during pregnancy, lactation, and after menopause. *Pathological* amenorrhea results from disorders of the HPO—uterine axis, endocrinopathies, psychological factors, drug usage, and other rare causes such as anatomic abnormalities, and genetic factors.

In clinical practice, it is helpful to consider amenorrhea as an abnormality in one of the four areas based on the underlying anatomic or endocrine dysfunction; viz. the hypothalamic, the anterior pituitary, the ovaries, and the outflow tract, including the uterus, cervix, and vagina. Investigating and treating the cause for amenorrhea can prove challenging because disorders at any of the above several hormonal levels can disturb the normal function and alter the pattern of menstruation or prevent it entirely. However, in the majority, diagnosis and management is usually straightforward,

\* For the purpose of evaluation, absence of any menses and secondary sexual characteristics by age 14 is defined as primary amenorrhea.

@ *Menopause* is defined as the terminal episode of naturally occurring menses; it's a retrospective diagnosis, usually made after 6 months of amenorrhea.

and a few need detail investigations, especially if fertility is desired but impaired.

## DIFFERENTIAL DIAGNOSIS

The causes for amenorrhea are grouped into primary and secondary, but these are shared between the two categories

### A—Primary Amenorrhea

#### Common

- Constitutional (i.e. physiological: delayed menarche and puberty)
- Severe psychogenic stress, depression
- Chronic illness
- Weight loss/lean body weight<sup>2,3</sup>
- Anorexia nervosa
- Heavy exercise.

#### Occasional

- Imperforate hymen<sup>#</sup>
- Vaginal septum
- Primary hypothyroidism, hyperthyroidism
- Diabetes mellitus (Type 1)
- Systemic disease (endometrial TB, malnutrition)
- Drugs (hormones, antiemetics, antihypertensives, antipsychotics).

#### Rare

- Pregnancy before menarche<sup>4</sup>
- Disorders of cerebral cortex (trauma, tumor)
- Disorders of hypothalamus (Kallmann's syndrome)
- Disorders of anterior pituitary (prolactinoma, Cushing's disease, Fröhlich syndrome, Laurence-Moon-Biedl syndrome, empty sella syndrome)
- Disorders of ovary (Turner's syndrome, polycystic ovarian syndrome, i.e. PCOS)
- Müllerian dysgenesis (uterovaginal agenesis)
- Chromosomal abnormalities (intersex, Turner's syndrome, testicular feminizing syndrome)

<sup>#</sup>Causes 'false' or 'cryptomenorrhea' — menstruation is taking place but the patient is unaware of it as the outflow is obstructed.

- Systemic disorders (autoimmune disease, adrenal tumor)
- Radiation, chemotherapy.

### B—Secondary Amenorrhea (Table 3.1)

#### Common

- Physiological (pregnancy, lactation, menopause)
- Functional hypothalamic amenorrhea (due to emotional, physical, social stress; depression)
- Drug-induced hyperprolactinemia (Table 3.2)
- Post-pill amenorrhea
- Infection (mumps, tuberculosis of the genital tract)
- Rapid weight loss (10-15%) or extreme obesity
- Anorexia nervosa, bulimia
- Surgery (hysterectomy)
- Endometrial ablation
- Progesterone IUD
- Polycystic ovarian syndrome (PCOS)
- Female athlete triad (*vide infra* ↓↓).

#### Occasional

- Premature ovarian failure (POF)
- Prolactin secreting adenoma
- Primary hypothyroidism
- Surgery, chemotherapy, radiotherapy.

#### Rare

- Disorders of pituitary (Sheehan's syndrome)
- Disorders of ovary (virilizing ovarian tumors, resistant ovarian syndrome)
- Disorders of genital outflow tract (Asherman's syndrome, Rokitansky-Küster-Hauser syndrome)
- Systemic disorders (autoimmune disease, adrenal tumors).

## INVESTIGATIONS—GENERAL

### Pregnancy Test

- All patients require an initial pregnancy test (serum or urine hCG). Any woman with amenorrhea is considered pregnant until proven

**Table 3.1:** Differential diagnosis of secondary amenorrhea

<i>Clinical scenario</i>	<i>Investigations</i>	<i>Comments</i>
<ul style="list-style-type: none"> <li>• Pregnancy possible</li> <li>• Galactorrhea, visual defect</li> </ul>	Serum, urine hCG elevated Prolactin elevated >100 ng/ml	Pregnant; no further testing  MRI – positive – Prolactinoma; MRI – Negative – other causes Drug-induced/other causes for
<ul style="list-style-type: none"> <li>• Symptoms of hypo-hyperthyroidism</li> <li>• Menopausal symptoms</li> </ul>	≤ 100 ng/ml prolactinemia (Table 3.2) THS, FT4 abnormal; prolactin normal dysfunction FSH elevated	Evaluate as indicated for thyroid  Primary ovarian failure; karyotyping if
<ul style="list-style-type: none"> <li>• Hyperandrogenic state</li> </ul>	Pelvic ultrasound–bilateral enlarged ovaries, subcapsular cysts; altered FH:FSH ratio >3:1; Testosterone >200 ng/ml DHEA-S and/or 17-alpha-OHP elevated	PCOS  Evaluate for adrenal tumor; congenital adrenal hyperplasia
<ul style="list-style-type: none"> <li>• None of the above</li> </ul>	Normal screening for hCG, prolactin, FH, FSH. a. Progesterin challenge test Positive Negative  b. Estrogen–Progesterin challenge test Positive   Negative	Chronic anovulation Evaluation further for other causes of secondary amenorrhea  Hypogonadotropic hypogonadism (constitutional delay, stress, weight loss, systemic disease, hypothalamic/ pituitary disorder, etc.) Anatomical or endometrial abnormality

**Table 3.2:** Causes of hyperprolactinemia<sup>#</sup>

<b>Physiological</b> <ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Breastfeeding</li> <li>• Breast stimulation</li> <li>• Sexual intercourse</li> <li>• Exercise</li> <li>• Stress (e.g. venesection, trauma, surgery, myocardial infarction)</li> </ul> <b>Pathological</b> (serum prolactin ≥ 100 ng/ml) <ul style="list-style-type: none"> <li>• Pituitary disease (e.g. Prolactinoma, nonsecreting adenoma, meningioma, metastasis)</li> <li>• Hypothalamic and pituitary stalk disease (e.g. TB, sarcoidosis, craniopharyngioma, empty sella, metastasis, cranial irradiation)</li> </ul> <b>Medications</b> <ul style="list-style-type: none"> <li>• Oral contraceptive pills</li> <li>• Antipsychotics</li> <li>• Antidepressants</li> <li>• Antihypertensives</li> <li>• Antiemetics</li> <li>• Histamine H<sub>2</sub> receptor blockers</li> </ul>
--

Contd...

Contd...

- Hormones
- Glucocorticoid excess
- Opiates, cocaine
- Altered Metabolism**
  - Liver failure
  - Renal failure
  - Seizures
- Ectopic production**
  - Bronchogenic (e.g. carcinoma)
  - Gonadoblastoma
  - Hypopharynx
  - Ovarian dermoid cyst
  - Renal cell carcinoma
  - Teratoma
- Others**
  - Hypothyroidism
  - PCOS
  - Addison's disease

<sup>#</sup>Normal serum prolactin reference range – ≤25 ng/ml; Hyperprolactinemia = serum prolactin ≥40 ng/ml (40 mcg/l)



otherwise; false-positive testing may occur vary rarely with ectopic hCG secretion (e.g. choriocarcinoma or bronchogenic carcinoma).

### US of Pelvis

- Anatomic abnormalities should be excluded before performing an endocrine evaluation. Pelvic ultrasound will evaluate for the presence or absence of pregnancy, ovarian cysts (PCOS), ovarian tumor, uterine lesions such as hematometra, Asherman's syndrome, and uterovaginal disorders.

### TFTs

- Hypothyroidism, including subclinical hypothyroidism, may affect menstruation, leading to amenorrhea. Besides, abnormal thyroid hormone levels can affect prolactin levels; therefore, measuring TSH, FT4 levels is indicated in patients with amenorrhea.

### ESR

- Elevated in autoimmune disorders; may be of significance in patients associated with POF.

### Blood Glucose

- Diabetes mellitus type 1 is associated with a higher incidence of hypogonadotrophic amenorrhea, secondary to chronic systemic illness, possibly due to derangement in HPO axis.

### Urea, Creatinine, Electrolytes, LFTs

- For assessing renal and hepatic disease, including alcoholism.

### RF, ANA

- For evidence of autoimmune disease associated with resistant ovarian syndrome.

## INVESTIGATIONS—SPECIFIC

### Physical Examination

- For evidence of structural abnormality of the genital tract, it should be performed earlier in investigation of primary amenorrhea.

### Endocrine Hormone Assays

- May include serum LH, FSH, serum prolactin, estradiol, free testosterone, 17-hydroxyprogesterone, and dehydroepiandrosterone sulfate (DEHA-S).

### Serum Prolactin (PRL — Normal Reference- <25 ng/ml)

- Level up to 100 ng/ml suggests hyperprolactinemia; more than 100 ng/ml occurs in the presence of a tumor. PRL levels fluctuate periodically, therefore, several measurements may be necessary to confirm hyperprolactinemia.

### Serum LH, FSH

- Elevated LH and FSH (>40 ml IU/ml) are suggestive of ovarian failure, e.g. POF, resistant ovary syndrome, or autoimmune ovarian failure. If FSH and LH levels are elevated, POF is the most likely cause
- An increased ratio of LH: FSH exceeding 3:1 suggests PCOS, and helps differentiating patients of PCOS from hypothalamic dysfunction
- Low LH and FSH values (<20 ml IU/ml) suggest physiological hypothalamic amenorrhea (stress, anxiety, diet, exercise) or pituitary disease (GnRH deficiency).

### DEHA-S

- Elevated DEHA-S suggests adrenal insufficiency or tumor.

### Free Testosterone

- Elevated values are seen in PCOS, ovarian tumor, adrenal tumor, and Cushing's syndrome.

### Progestin Challenge (Withdrawal) Test

- This test is performed to confirm the presence of adequate endogenous estrogen (>50 pg / ml). Medroxyprogesterone acetate 10 mg is given orally once daily for 5-7 days or injection progesterone in oil 100 mg intramuscularly. Any withdrawal bleeding occurring within 2 days to 2 weeks following the final dose indicates that the



patient has sufficient estrogen, suggesting that the major components of the hypothalamic, pituitary, ovarian, and uterine pathways are at least minimally functioning. The amenorrhea is likely caused by anovulation. The common underlying causes are hypothalamic dysfunction and PCOS. Absence of withdrawal bleeding during the week following after the final dose indicates estrogen deficiency or possibly outflow tract abnormality.

#### **Estrogen-progestin Challenge (Withdrawal) Test**

- This test helps to differentiate outflow abnormalities from estrogen deficiency. Estrogen is given for 21-25 days and a progestational agent for the final 5-7 days of estrogen therapy to stimulate withdrawal bleeding. If no bleeding occurs, an outflow tract abnormality (uterine agenesis, imperforate hymen) is present. If bleeding occurs, estrogen deficiency (due to hypothalamic, pituitary cause) is present and further testing is necessary.

#### **Dexamethasone Suppression Test**

- To screen for Cushing's syndrome and to differentiate disorders causing hypercortisolism without Cushing's syndrome (i.e. pseudo-Cushing's syndrome) such as in alcoholism, depression, anorexia nervosa, and antiseizure drugs.

#### **MRI/CT Scan — Brain**

- Hyperprolactinemia (i.e. serum prolactin > 100 ng/ml) warrants MRI of the brain. Various tumors such as craniopharyngiomas and meningiomas may cause hyperprolactinemia, but pituitary adenomas are the most common.

#### **Karyotyping**

- If LH and FSH levels are high, POF is the most likely explanation. In patients <30 years age or stigmata of Turner's syndrome, karyotyping is indicated to determine the chromosomal sex. If a Y chromosome is found, the chance of a gonadal malignancy is greatly increased.

#### **Laparoscopy**

- In PCOS, laparoscopy reveals bilateral enlarged ovaries with thickened tunica albuginea and multiple cystic follicles.

#### **Hysteroscopy**

- Helps to establish the diagnosis of Asherman's syndrome.

### **CLINICAL NOTES**

- The clinical evaluation of the patient should include careful history, and should always include the following:
- Menstrual history, including dates of last menstrual period—Age of menarche is important and separates primary amenorrhea from secondary amenorrhea. A history of cyclical abdominal colicky pain, retention of urine suggests cryptomenorrhea presenting as primary amenorrhea. Sudden missed menses preceded by regular menses suggests pregnancy in reproductive-age woman. Oligomenorrhea progressing gradually to amenorrhea characterizes PCOS
- Additional history may include symptoms of: Pregnancy (nausea, breast tenderness, weight gain); menopause or premature ovarian failure (hot flushes, vaginal dryness, mood changes); headache, visual disturbances, galactorrhea (prolactinoma); seborrhea, acne, excessive coarse hair growth, voice change (hyperandrogenism, mostly caused by PCOS); anosmia (Kallmann's syndrome)

- Medications (Table 3.2) may induce hyperprolactinemia. Post-pill amenorrhea may persist for several months
- Vigorous exercise—A history of excessive activity level suggests the *female athlete triad* (i.e. amenorrhea, eating disorder, and osteoporosis: *vide infra* ↓↓)
- Social history includes—Dietary habits, ‘crash’ dieting, nutritional status, weight loss, emotional and physical stress, and sexual activity
- Family history includes—Family pattern of sexual development (menarche of mother and sisters), genetic anomalies, and endocrinopathies (diabetes, thyroid dysfunction)
- Past history includes—Trauma, surgery (hysterectomy), endometrial curettage, infection (TB), chemotherapy, and irradiation
- Physical examination—This is guided by history and should address the following:
  - Psychologic status (stress, depression)
  - BMI,<sup>§§</sup> nutritional status, height (short stature in Turner’s syndrome)
  - Secondary sexual characteristics (Tanner staging: Table 3.3)
- The type and stage of development of secondary sexual characteristics such as breast and areola development, axillary and pubic hair growth, provide most important guide to diagnostic work-up in patients with primary amenorrhea
- Associated symptoms and signs as clues to the diagnosis include:
  - Signs of hirsutism (acne, excessive facial and body hair), virilization (voice change, temporal baldness) are suggestive of PCOS and ovarian or adrenal tumor.
  - Expressive galactorrhea suggests hyperprolactinemia.
  - Anosmia with hypogonadism suggests Kallmann’s syndrome.
  - Visual field defects on confrontation indicate pituitary adenoma.
  - Features of Turner’s syndrome may be present.

<sup>§§</sup>Menstruation fails to occur regularly if BMI falls below 18-19 kg/m<sup>2</sup> and it is estimated that 22% of female body weight should be fat to ensure ovulatory cycle.

**Table 3.3:** Tanner staging for female secondary sexual characteristics

Stages of breast (B) development	Stages of pubic hair (PH) development
<ul style="list-style-type: none"> <li>• B1 preadolescent, elevated papilla, small flat areola</li> <li>• B2 (age 11, range 8-13) breast bud, papilla and areola elevate, increased areolar diameter</li> <li>• B3 (age 12) continued enlargement of breast bud, no separation of breast contours</li> <li>• B4 (age 13) areola and papilla separate from contour of breast to form secondary mound</li> <li>• B5 (age 15, 13-18) mature, areolar mound recedes into general contour of breast, papilla continues to project</li> </ul>	<ul style="list-style-type: none"> <li>• PH 1 preadolescent, no pubic hair, fine vellus hair covers genital area</li> <li>• PH 2 (age 11) sparse distribution of long slightly pigmented straight hair bilaterally along medial border of labia majora</li> <li>• PH3 (age 12) pubic hair increases in pigmentation, begins to curl and spread sparsely over mons pubis</li> <li>• PH4 (age 13) pubic hair continues to curl and becomes coarse, increase in number</li> <li>• PH 5 (age 14) mature, pubic hair attains triangular pattern, spread to surface of medial thigh</li> </ul>

- Pelvic examination—Physical findings may be grouped as below:
  - In primary amenorrhea:
    - External genitalia (male or female)
    - Clitoromegaly<sup>\*\*\*</sup>
    - Imperforate hymen
    - Absent or blind ending vagina
    - Uterus and cervix (present or absent)
  - In secondary amenorrhea:
    - Clitoromegaly
    - Atrophy of vulva and vaginal skin
    - Uterine size
    - Ovarian tumor
- Systemic examination—For evidence of Turner’s syndrome, hypo- and hyperthyroidism, Cushing’s disease, panhypopituitarism, chronic hepatic or renal disease. Evidence of autoimmune disorder (RA, SLE, and myasthenia gravis) is suggestive of autoimmune ovarian failure
- Primary amenorrhea with normal secondary sexual characteristics is commonly due

<sup>\*\*\*</sup>Clitorimegaly defined as a length times width product of greater than 40 mm<sup>2</sup>.

to anatomical defects and rarely due to androgen insensitivity syndrome, i.e. patient phenotypically female but genetically male with undescended testes. A karyotype analysis is needed to determine proper treatment. If testes are present, they should be removed because of the high risk of malignant transformation after puberty

- Primary amenorrhea with hypoplastic secondary sexual characteristics is commonly due to HPO axis disorders; Turner's syndrome is the commonest type of dysgenetic gonad.

### RED FLAGS

- Although primary pregnancy before menarche is extremely rare, it's not impossible. "Although the first few menstrual cycles after menarche are often anovulatory, this is not always the case. Because it is no longer uncommon for girls to be sexually active in their early to mid teens, a sensitive discussion of this subject and a pregnancy test are necessary in the initial investigation of amenorrhea in women of almost any age"<sup>5</sup>
- Although 'constitutional delay of menarche and puberty' is a common cause for primary amenorrhea, it should not be assumed to account for amenorrhea; periodic follow up to evaluate other pathological causes for delayed puberty (e.g. growth velocity for skeletal age) is indicated
- In patients with secondary amenorrhea, physical and pelvic examinations must rule out pregnancy before diagnostic testing begins
- Oral contraceptives do not cause amenorrhea after discontinuation. Amenorrhea occurring after discontinuation of oral contraceptive therefore needs the same investigations as amenorrhea temporarily unrelated to previous use of an oral contraceptive.

### SELECTIVE GLOSSARY

**Female athlete triad**—Includes "amenorrhea, osteoporosis and eating disorders. The incidence of menstrual irregularities including primary and

secondary amenorrhea and shortened luteal phases is much higher among women partaking in athletics, specifically in sports requiring low body weight for performance and aesthetics. The hormone pattern seen in these amenorrheic athletes includes a decrease in GnRH pulses from the hypo-thalamus, which results in decreased pulsatile secretion of LH and FSH and shuts down stimulation of the ovary. The recently discovered hormone leptin may also play a large role as a significant mediator of reproductive function. The prevalence of eating disorders is high among female athletes who practice sports which emphasize leanness. Consequently, the cause of menstrual irregularities is not due to the exercise alone, but to chronic inadequate or restrictive caloric intake that does not compensate for the energy expenditure. The most dangerous risk associated with amenorrhea for the female athlete is the impact on the skeleton. Complications associated with amenorrhea include compromised bone density, failure to attain peak bone mass in adolescence and increased risk of stress fractures. The diagnosis of exercise-associated menstrual dysfunctions is one of exclusion. The most effective treatment is to decrease the intensity of the exercise and increase the nutritional intake. Hormone replacement has also been under investigation as a possible treatment".<sup>6</sup>

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## CHAPTER

# 4

## Anxiety

### SYNOPSIS

In clinical practice, a significant number of patients presenting with psychiatric symptoms seek an acceptable explanation and relief from symptoms or illness. These symptoms are either quantitatively excessive (compared with normal reaction to stress), or qualitatively abnormal (they do not usually occur as understandable reaction to stress). For many patients such episodes of illness represent major disruption to life; they may even express fears for their own mortality. All these are essentially normal and understandable responses to the illness and the context in which they occur, and a normal individual deals with such fears or apprehensions effectively by utilizing his inherent defence mechanisms that produce a natural 'fight-or-flight' adaptive response. However, in some the defensive mechanism is inadequate, leading to a maladaptive response, resulting in overt emotional, behavioral and physical manifestations, which can vary enormously from feeling tense or tired to panic attack. Thus, the experience of an unpleasant and inappropriate *affective state* (i.e. fear or apprehension out of harmony with the idea, thought, or object accompanying it) with the expectation of, but not the certainty of something untoward happening is defined as *anxiety*\*. A definition which is briefer and to the point is: 'a fear for no adequate reason'.<sup>1</sup>

Anxiety is always accompanied by disturbances of autonomic functions, and because the patients are not aware of the relation between their anxiety and other symptoms, the latter usually dominate the clinical picture. Patients may present with any of the complaints (Table 4.1), but particularly common are headache, dizziness, chest pain, palpitation, abdominal cramps, diarrhea, tremor, fatigue, and emotional upset. There is often an increase in tone in voluntary muscles, so that the patient has a sense of tension and complains of feeling tense, keyed-up, on edge, unable to relax, lack of concentration, irritable, and insomnia. When anxiety becomes intense, chaotic motor behavior may occur, which is usually called *panic*; the patient may experience choking or smothering, feeling of dead or threat, which may lead the patient to associated comorbid disorders.<sup>†</sup>

The evaluation and management of anxiety

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\* Anxiety is sometimes differentiated from fear, as anxiety is a feeling of unease or dread in response to an *internal* stimulus, in contrast to fear, which is based on an *external* threat.

†In certain individuals anxiety may extend beyond the single issue of their worry and may lead to phobias, obsessive compulsive disorder, panic disorders, hypochondriasis, and somatization.

**Table 4.1:** Clinical features of anxiety: emotional/psychological symptoms

• Apprehension/fearful anticipation	• Behavioral problems (especially in children and adolescents)
• Irritability	• Nervousness and jumpiness
• Impaired concentration/ 'mind going blank'/ impatience	• Exaggerated startle response
• Feeling restless/on edge	• Fear that you are dying/ 'going crazy'
• Confusion	
• Insomnia	

can be challenging because patients present with distress and concern about disease in the absence of objective evidence. However, "...central to the whole issue of diagnosing anxiety disorders, it is usually not the illness that is masked but the doctor who is blind. By confining enquiries to physical systems, the correct questions are not asked, and consequently the correct diagnosis is missed..."<sup>2</sup> Also, anxiety and anxiety-like symptoms may be consequent to a variety of medical ailments and their treatment (Table 4.2).<sup>3</sup> Therefore, a comprehensive, emphatic understanding, and time to listen to the patient permits a reasoned and often a therapeutically effective approach to the difficult problem.

## DIFFERENTIAL DIAGNOSIS

### Common

- Acute stress reaction (death; accident; traumatic diagnosis: HIV, ESRD, end-stage COPD; cancer; assault; rape)
- Adjustment reaction with anxiety (interpersonal conflict)
- Psychiatric disorder (generalized or chronic anxiety state, depression, hyperventilation syndrome)
- Acute systemic illness (acute coronary syndrome, bronchial asthma, stroke, seizure, migraine)

**Table 4.2:** Anxiety and anxiety-like state

#### A-Medical conditions which can mimic or cause anxiety

- Hypertyroidism
- Hypoglycemia
- Hyperventilation syndrome
- Asthma
- Sleep disorders
- Trauma
- Adrenal disorders
- Temporal lobe epilepsy
- Cardiac—acute coronary syndrome, MVP
- Psychiatric illnesses—depression

#### B-Medications and substances which can induce anxiety

- Stimulant drugs (Caffeine and other stimulants)
- Abuse drugs (heroin, cocaine, amphetamine)
- Over-the-counter medications (decongestants)
- Steroids
- Hormones (oral contraceptives, thyroid medication)
- Bronchodilators and respiratory inhalers
- Herbal remedies (ephedra)
- Hypertensive medication
- Withdrawal from alcohol
- ADHD medications (amphetamine)
- Withdrawal from benzodiazepines (Diazepam)

- Substance abuse (alcohol, benzodiazepines, caffeine)
- Menopause.

### Occasional

- Medications (bronchodilators, antipsychotics, amphetamine, insulin)
- Drug withdrawal (anxiolytics, sedatives, hypnotics)
- Chronic systemic disease (diabetes mellitus, cardiac arrhythmia, hyperthyroidism, rheumatoid arthritis, hepatitis B and C, post-herpetic neuralgia)
- Psychiatric disorders (panic, phobia, obsessive compulsive disorder, post traumatic stress disorder, hysteria, psychosis, dementia).

### Rare

- Systemic disorders (mitral valve prolapse, pheochromocytoma, Cushing's disease)
- Secreting tumors (carcinoid, insulinoma)



- Metabolic (electrolyte disorders, porphyria).
- Anaphylaxis.

## INVESTIGATIONS—GENERAL

### Blood Glucose

- In diabetic patients on insulin and/or sulfonylureas, plasma glucose <50 mg/dl causes hypoglycemic episodes leading to adrenergic symptoms such as anxiety, palpitations, and tremor
- Asymptomatic fasting hypoglycemia may indicate primary pancreatic  $\beta$  cell dysfunction, typically a  $\beta$  cell tumor—insulinoma.

### Thyroid Profile

- Decreased levels of TSH with increased levels of FT4 suggest thyrotoxicosis.

### ECG

- Useful to evaluate possible tachyarrhythmias, coronary syndromes, and to screen for drug-induced QT prolongation.

## INVESTIGATIONS—SPECIFIC

### 24-hour Urine for Catecholamines

- Increased levels of VMA and HMMA in urine, or increased levels of free metadrenaline in urine and blood (soon after episode of anxiety symptoms) is suggestive of pheochromocytoma.

### Serum Insulin/C Peptide

- May be indicated if insulinoma is strongly suspected.

### 24-hour Holter Monitor

- To exclude paroxysmal cardiac arrhythmia.

### CT Scan/MRI Pancreas

- May be useful to detect pancreatic  $\beta$  cell tumor, e.g. insulinoma.

### EEG

- Patients with intermittent anxiety with period of remission in between the episode should have a wake-and-sleep EEG (and possibly a CT) to rule out cerebral tumor.

## CLINICAL NOTES

- Anxiety is a normal human emotion. Distinguishing normal anxiety from pathologic anxiety and anxiety disorders<sup>†</sup> often requires systematic evaluation and a thorough understanding of the individual patient's physical and psychological status
- Also, it cannot be assumed that physical symptoms are simply secondary to an anxiety disorder because anxiety may be the consequence of a physical illness such as in the cardiac or hyperthyroid patient. Anxiety may also coexist with other psychiatric disorders as in bipolar depression. Hence it is important to be certain about the diagnosis of anxiety *per se*
- Typical features of *pathological* anxiety include excessive, unrealistic, and persistence of its somatic and physical symptoms (Table 4.3) for more days than not, for at least six months, *in the absence of an objective stimulus*. The focus of anxiety may be everyday trifle activities (e.g. appointment, communication) or life events (e.g. job performance, marriage relationship, financial stability, and retirement)
- Diagnosis of anxiety is based on the history—It is vital to listen carefully to what patients' say; it helps to determine whether their

<sup>†</sup>As outlined in the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV), anxiety disorders include generalized anxiety disorder (GAD), social anxiety disorder (SAD, also known as social phobia), specific phobia and panic disorder (PD), with and without agoraphobia, obsessive-compulsive disorder (OCD), somatization and post-traumatic stress disorder (PTSD).

**Table 4.3:** Pathological anxiety: signs and symptoms

<i>Motor tension</i>	<i>Autonomic overactivity</i>
Muscle tension or ache	Dry mouth
Tension headaches	Palpitation/tachycardia
Tremors, twitches, and jitters	Sweating/cold clammy skin
Tiredness/fatigue	Flushes/chills
	'Lump in throat'/difficult swallowing
	Diarrhea/abdominal distress
	Frequent urination
	Difficulty breathing/suffocating
	Dizziness/light headedness

anxiety is dysfunctional, i.e. whether it is excessive and sustained and interferes with daily living. History also helps to ascertain if medications, substance abuse, a medical illness, or associated psychiatric disorder is aggravating patient's anxiety. Historical data from family members may indicate the cause of acute anxiety

- History of intermittent anxiety—Suggests cardiac arrhythmia such as PSVT or AF, psychomotor epilepsy, insulinoma, and pheochromocytoma
- Age—The young and the middle-aged patient is more likely to suffer from a psychiatric disorder, while older patient may be suffering from vascular or some other form of dementia
- Physical examination—Patient with anxiety is restless, agitated; vital signs reveal tachycardia and increased blood pressure and respiration; neurologic examination usually shows brisk tendon reflexes and tremors. Sustained tachycardia with weight loss makes hyperthyroidism a very likely possibility. Presence of a thyroid bruit, auscultatory systolic click indicates hyperthyroidism and mitral valve prolapse respectively
- Exclusion of other psychiatric disorders, especially depression—The Mini Mental State Examination (MMSE) protocol is useful to screen patients for this purpose. It is

critical to diagnose depressive disorders because they are common, treatable, carry a high risk of morbidity and mortality, and frequently coexist with anxiety. In addition DSM IV criteria may be used to determine specific psychiatric disorder.

## RED FLAGS

Anxiety and depression frequently occur together, which can complicate the clinical picture, including suicidal attempts or self-medication with alcohol or other illicit drugs.<sup>4-7</sup>

Cardiac arrhythmias, endocrinopathies (insulinoma), and medication reactions constitute significant number of undiagnosed psychiatric referrals for 'anxiety'.

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## CHAPTER

# 5

## Arthralgia and Arthritis

### SYNOPSIS

*Arthralgia* is pain or discomfort in one or more joints. Apart from tenderness, abnormalities of the joint cannot be identified.

*Arthritis* is painful joint with associated signs of inflammation such as erythema, swelling, tenderness, effusion, and limitation of movements of the joint. Often, both arthralgia and arthritis coexist in the same joint;\* arthralgia being an early symptom whose clinical signs is not yet apparent or too subtle for detection.

Joint pain can be a manifestation of disorders confined to the joint and also of a number of systemic disorders. Identifying the cause of joint pain, therefore, can be difficult because of extensive differential diagnosis. In some cases the diagnosis may be hindered by atypical presentation (as in the elderly or immunocompromised), or masked in those with multiple comorbidities and/or symptoms. Consequently, it is prudent to keep the diagnosis open in patients who present with pain in multiple joints. For instance, what may begin as a monoarthritis may in course of time become polyarthritis, thereby necessitating a review of

alternative diagnostic possibilities. Similarly, an elderly woman, diagnosed initially as RA, may later develop a malar rash and oral ulcer which would change the diagnosis to SLE.

A careful history and physical examination are essential which will help guide appropriate investigations and management. The most relevant aspects to decide are threefold:

1. Whether the underlying disorder is inflammatory or not (Table 5.1).
2. Establish the type of onset (acute or otherwise), and its subsequent evolution (i.e. self-limiting, monoarticular, polyarticular symmetrical, or polyarticular nonsymmetrical: Table 5.2).
3. The presence of associated extra-articular and systemic manifestations (e.g. fever, rash, eye involvement, bowel symptoms, Raynaud's, etc.)

The majority of conditions are benign and self-limiting, but a minority (trauma, sepsis, gout) may require an urgent assessment and treatment.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Infection (viral: adenovirus, parvovirus—especially B19, alphavirus<sup>1,2</sup> For example:

\*The term *arthrosis* is sometimes used to describe a degenerative lesion of a joint.

**Table 5.1:** Differentiating inflammatory arthritis from noninflammatory (usually degenerative) arthritis

Features	Inflammatory arthritis	Noninflammatory arthritis
Synovial WBC count	>2000/ $\mu$ l	<2000/ $\mu$ l
-ESR, CRP	- Elevated	- Usually normal
-Early morning stiffness	- Prolonged; >1 hr	- 'Gel phenomenon' observed, i.e. pain and stiffness lasting few minutes after a period of joint immobility, and improves with mild to moderate activity.
Nights worse than days	Yes	No
Constitutional features (e.g. fever, fatigue, weight loss)	Yes, in certain conditions	No
Spontaneous disease flares	Common	Uncommon

chikungunya, dengue; bacterial—gonococcal, nongonococcal, e.g. staphylococcal, streptococcal; tubercular)

- Osteoarthritis
- Rheumatoid arthritis
- Trauma.

#### Occasional

- Infection (Brucellosis; viral: HBV, HCV, HIV; Lyme disease)
- Gout, pseudogout
- Reactive arthritis (i.e. Reiter's syndrome<sup>†</sup>)
- Prosthetic joint arthritis (bacterial, tubercular, fungal)
- Adult onset Still's disease (Juvenile rheumatoid arthritis).

#### Rare

- Rheumatic fever with arthritis
- Spondyloarthropathies (ankylosing spondylitis, i.e. AS; Reiter's syndrome; Psoriatic arthritis, IBD)

<sup>†</sup> Of historical interest is the fact that this diagnosis shares its name with the man who first described it, Hans Reiter, a Nazi physician who tested unapproved vaccines and performed experimental procedures on victims in concentration camps. The infamous legacy of Reiter's name has led to the proposal that the syndrome be referred to by another, more descriptive name such as Reactive arthritis.

**Table 5.2:** Pattern of joint involvement and differential diagnosis

- Monoarticular—Acute
  - Septic arthritis (gonococcal, nongonococcal, or viral)
  - Gout (due to uric crystal deposition)
  - Pseudogout (due to calcium pyrophosphate crystal deposition)
  - Hemarthrosis
  - Acute presentation of seronegative spondyloarthropathies, e.g. Reactive arthritis
- Monoarthritis—Subacute or chronic
  - Tuberculosis
  - Postinfective arthropathies (mostly viral)
  - Osteoarthritis
  - Trauma
  - Rheumatoid arthritis (i.e. palindromic onset)
  - Juvenile chronic arthritis
  - Malignancy
- Polyarticular—Asymmetrical
  - Seronegative spondyloarthropathies:
  - Ankylosing spondylitis
  - Reiter's disease
  - Psoriatic arthritis
  - Enteropathic arthritis (associated with IBD)
- Polyarticular—Symmetrical
  - Rheumatoid arthritis
  - Osteoarthritis
  - Arthritis associated with autoimmune rheumatic disease:
  - Systemic lupus erythematosus
  - Scleroderma
  - Vasculitis
  - Sjögren's syndrome (primary)
  - Antiphospholipid syndrome
  - Dermatomyositis/polymyositis
  - Polyarticular septic arthritis
  - Poncet's disease (*vide infra* ↓↓)
  - Polyarticular gout—
  - Arthritis associated with malignancy
  - Miscellaneous—sarcoidosis, amyloidosis

- Collagen disease (SLE, PAN, PMR, scleroderma)
- Immune-mediated (serum sickness, lepra reaction)
- Hematologic (hemophilia, sickle cell disease, leukemia)
- Malignancy (hypertrophic pulmonary osteoarthropathy, i.e. HPOA; metastasis).

## INVESTIGATIONS—GENERAL

### CBC

- Hb reduced in inflammatory arthritis; leukocytosis in osteomyelitis, reactive arthritis, and acute gout; and eosinophilia in collagen arthropathies, e.g. SLE, PAN.

### ESR, CRP

- Most useful in the assessment of patients with RA, PMR, and giant cell arthritis; however, their values are elevated in a wide variety of disorders, including infections, trauma, inflammatory arthritides and various neoplasms.

### RF

- IgM RF may be positive in the majority of patients with RA.

### Serum Uric Acid

- Values are elevated at some point during acute attack, though a single estimation is normal in up to 25% of acute gouty patients.

### X-rays

- Bone and/or joint X-rays are indicated in all cases of major trauma to exclude fracture; to diagnose pathological fracture such as in osteomalacia, bone metastasis, and to diagnose stress fracture. Other radiological features of common arthritic disorders are given in Table 5.3.

## INVESTIGATIONS—SPECIFIC

### ASO Titer

- In patients with rheumatic fever the ASO titer is useful to document evidence of a preceding streptococcal infection.

### Blood Culture

- In septic arthritis.

**Table 5.3:** Radiographic findings in common arthritis

Disease	Findings in target joints
Acute osteomyelitis	Initially normal; localized soft-tissue swelling, bone destruction, involucrum, sequestrum, cloaca formation seen as disease advances
Osteoarthritis	Joint space narrowing; subchondral sclerosis, osteophytes, cysts; effusion; varus or valgus deformities in weight-bearing joints. Growth of osteophytes is one of the best indicators of disease progression.
Rheumatoid arthritis	Target areas include all five MCP, PIP joints, and all wrist compartments and feet. Joint space widening is the earliest and very transient finding (due to effusion). Other early features include periarticular swelling, regional osteoporosis, and erosion near joint capsule. Late signs are joint space narrowing, periarticular erosion, extensive destruction of bone ends, bony fusion, and cyst formation.
Psoriatic arthritis	Almost always accompanies skin disease, especially nail changes; mostly involves DIP joints of hand, classical deformity is called “cup-and-pencil deformity”. Involvement of MTP and interphalangeal joints of feet may cause “ivory phalanx”
Gout	Often unremarkable early in disease. Later “punched-out” lytic bone lesion with sclerosis, interosseous tophi, and calcium deposits in soft tissues.
Pseudogout (CPPD)	Most frequent in the knees; calcification in the hyaline and fibrocartilage (chondrocalcinosis) is present.
Ankylosing spondylosis	Sacroiliac joint involvement. Sacroiliitis occurs early with “saw-teeth” appearance. Initially the joint may look widened; squaring of the lumbar vertebral bodies is characteristic; followed by “bamboo-spine” appearance.

### ANA

- A positive ANA does not confirm diagnosis of SLE; a negative value virtually excludes the diagnosis of SLE and drug induced lupus.

**Anti-double-stranded DNA (Anti-dsDNA) Antibody**

- Almost diagnostic of SLE; occasionally found in other conditions, e.g. RA, drug-induced lupus, autoimmune hepatitis and lupus nephritis.

**Anti-Smith (Anti-Sm) Antibody**

- Diagnostic of SLE.

**Cytoplasmic Antineutrophilic Cytoplasmic (C-ANCA) Antibody**

- Positive in vasculitis, e.g. Wegener's granulomatosis.

**Cyclic Citrullinated Peptide (CCP) Antibody**

- Positive in RA.

**Human Leukocyte Antigen (HLA - B27) Typing**

- Positive in spondyloarthropathies, especially AS.

**HLA DR4/ DR1 Typing**

- In the initial diagnosis of RA; its presence is associated with poor prognosis.

**Serology**

- For evidence of HBV, HCV, HIV, and Lyme disease.

**TFTs**

- For evidence of hyperthyroidism or hypothyroidism.

**US with Duplex Scanning**

- Helpful in imaging small structures or subtle abnormalities such as partial ligament or tendon tears; synovial inflammation, hypertrophy, or effusions; and articular

cartilage lesions. High-resolution ultrasonography (HRUS) allows detailed 'real time' imaging of joint and tendon morphology, and structural changes involving the hand in patients with several rheumatic diseases, including RA, SLE, and gout, even in clinically silent joints.<sup>3-5</sup>

**CT/MRI**

- CT to diagnose fractures, infection, neoplasm, and vascular necrosis; MRI is best for assessing soft-tissue and spinal-cord elements.

**Synovial Fluid Analysis**

- Provides valuable information, especially in patients with monoarthritis and joint effusion. Gouty arthritis is definitely diagnosed in the presence of urate crystals. Other parameters such as cell count and culture studies help to differentiate inflammatory arthritis from non-inflammatory and septic arthritis.

**Synovial Biopsy (Diagnostic Arthroscopy)**

- May be essential in the diagnosis of granulomatous arthritis such as tuberculosis, sarcoidosis, amyloidosis, synovial tumors, or mycotic infections.

**CLINICAL NOTES**

- When an individual presents with complaints of musculoskeletal aches and pains, it is prudent to ascertain that the symptoms confirm to 'arthritis', because what may apparently look like an arthritic condition may actually be a manifestation of '*soft tissue rheumatism* (STR)<sup>‡</sup>, also known as 'non-articular rheumatic pain syndrome'. For

<sup>‡</sup> STR is a collection of nonarticular pain generators that result from pathology of extra-articular and extraosseous periarticular structures. These soft tissue structures include bursae, tendons and their synovial sheaths, entheses, muscles and fasciae.

example, ‘pain in the knee’ as the patient may complain, may actually be due to pain because of bursitis over the knee; ‘pain in the shoulder’ may be due to adhesive capsulitis as against arthritis in the shoulder joint. The main features that differentiate arthritis and STR are explained in Table 5.4.

- The most useful information in evaluating joint pain comes from history and physical examination. The relevant aspects are age; whether the underlying condition is inflammatory or degenerative; type of onset (i.e. acute or otherwise); subsequent evolution (i.e. self-limiting, monoarticular, polyarticular symmetrical, or polyarticular non-symmetrical); and presence of associated or complicating extra-articular features.

**Table 5.4:** Difference between arthritis and STR

Clinical features	Arthritis	STR
Pain	Deep, diffuse, around area of affected joint	Superficial and localized around affected bursa, tendon, muscle, etc.
Tenderness	Circumferential around the joint where capsule is accessible to surface	Localized to the site of affected structure
Effusion	Develops with more advanced disease	Usually superficial swelling; effusion rare
Pain on active range of motion (ROM)	Present	Absent
Pain on passive ROM	Present	Absent
Instability/deformity	Often present	Absent

- Age—Infectious causes as well as trauma have no particular age association. SLE presents between second and fourth decades of life; RA is more common between fourth and sixth decades; and OA peaks in the seventh and eighth decades
- Duration—Joint disorders are acute or chronic, i.e. either less or more than six weeks respectively. Acute disorders are often traumatic, infectious, metabolic (gout), or reactive; chronic disorders often include noninflammatory and immunologic disorders such as OA and RA. However, an acute

episode may be a harbinger of a chronic polyarticular disease, and a chronic condition can present as an acute episode. Therefore, chronic conditions such as RA, SLE, and gout should be considered, at least initially, in patients who present with acute polyarticular or monoarticular joint pain

- Inflammatory or degenerative etiology—Inflammatory features include the presence of all or some of the cardinal signs of inflammation (i.e. erythema, warmth, pain, swelling, and morning stiffness), and generally associated with systemic symptoms (e.g. fever, fatigue, weight loss). Common examples are infections, RA, gout, and reactive arthritis. Degenerative (i.e. noninflammatory) features include pain without swelling or warmth, activity-related pain, minimal or absent morning stiffness, and absence of systemic symptoms. Common examples are OA, fibromyalgia, and neoplasms
- Affected joints—Early OA can present in one joint, most commonly the knee. Podagra, or pain in the first metatarsophalangeal joint, is the classic presentation of gout, appearing suddenly at night. Gout most commonly affects joints in the feet, ankles, hands, wrists, elbows, and knees; less commonly affected areas include the sacroiliac, sternoclavicular, and shoulder joints. Gout rarely affects the hip and spine. Symmetrical involvement of metacarpal phalangeal, proximal interphalangeal joints, wrist, and feet is more common in RA; involvement of knees and hips is unusual. OA favors knees, ankles, feet, and spinal column, but involvement is not necessarily symmetrical. Depending upon the underlying cause, the pattern of arthritis may change overtime
- Lifestyle factors—Diet rich in purine foods (liver, kidney, red meat) and alcoholism can precipitate an attack of gout in susceptible individuals. High-risk behaviors, intravenous

drug use, past history of STD are risk factors for infectious arthritis, including viral hepatitis and HIV

- Medications—Diuretics, chemotherapeutic agents, niacin, and aspirin can precipitate gout. Hydralazine, isoniazid, methyldopa, procainamide, chlorpromazine, and quinidine are known to cause a lupus-like syndrome
- Family history—RA, SLE, OA, ankylosing spondylosis, and (primary) gout have a familial component. SLE is also found in families with other autoimmune disorders such as hemolytic anemia, thyroiditis, idiopathic thrombocytopenic purpura, vitiligo, and antiphospholipid antibody syndrome
- Extra-articular symptoms and systemic manifestations are often helpful in narrowing the differential diagnosis (Table 5.5).

## RED FLAGS

- Arthritis caused by alpha viruses, especially Ross River, Chikungunya and Pogosta disease is increasing, and these should be kept in mind as a possibility, especially in those cases where the disease starts with flu-like symptoms, and rash is involved
- Beware of the *red-hot joint* (Table 5.6), i.e. a single acutely inflamed, swollen joint that may present a diagnostic problem. For example, acute gout is often confused with cellulitis; joint aspiration and bacteriological studies are indicated for precise diagnosis
- Pain in wrists and ankles in a middle-aged or elderly smoker with new onset of digital clubbing strongly suggests HPOA caused by underlying bronchogenic carcinoma
- Persistent underlying bone or skeletal pain, nocturnal pain, swelling, and spontaneous fracture warrants prompt evaluation to exclude malignancy (usually secondaries) and leukemic arthritis.

**Table 5.5:** Clinical signs associated with arthritis and systemic disease

Signs	Disease association
Eyes	
Conjunctivitis	Gonococcal/Reactive arthritis
Episcleritis/scleritis	RA, vasculitis
Uvulitis/iritis	Spondyloarthropathies
Keratitis sicca	Sjögren syndrome
Skin, Nails, Mucous membrane	
Butterfly rash on face	SLE
Hypopigmented anesthetic patch	Leprosy, acute lepra reaction
Plaques	Psoriasis
Nodules / tophi	RA, Gout
Thickened skin	Scleroderma
Photosensitivity	SLE
Petechiae, purpura	Henoch-Schönlein purpura
Transient, superficial	SLE, Behçet's disease
Oral ulcer	
Jaundice	Hepatitis
Nails pitting, dystrophy	Psoriatic arthritis
Clubbing	Metastatic lung cancer, endocarditis
Head, ENT	
Hair thinning, alopecia	Hypothyroidism, SLE
Scalp tenderness	Giant cell arteritis
Parotid enlargement	Sjögren's syndrome
Sinusitis, epistaxis	Wegener's granulomatosis
Macroglossia	Amyloidosis
Heart, lungs	
Pericarditis, endocarditis	RF, RA
Pleuritis	TB, SLE, RA
Parenchymal lung	RA, PAN, SLE, sarcoidosis
Infiltration	
Hilar lymphadenopathy	Sarcoidosis, SLE
Abdomen, genitourinary	
Enteritis, colitis	IBD
Hepatosplenomegaly	RA, SLE, Felty's syndrome
Nephropathy	SLE
Calculi	Gout
Proteinuria, hematuria	SLE, vasculitis, infective endocarditis
Urethritis, cervicitis	Gonococcal, reactive arthritis
Neurologic	
Loss of pain and deep	Neurogenic arthropathy, Tabes,
Sensation	Hansen's disease, diabetes
Seizures	SLE
Facial palsy	Lyme disease

- Presence of HIV infection should be ruled out in a patient with Reiter's syndrome, (i.e. Reactive arthritis—a clinical tetrad of urethritis, conjunctivitis or uveitis, mucocutaneous lesions, and aseptic arthritis), who belong to high risk group for HIV infection.



**Table 5.6:** The red-hot joint

- Infectious
  - Bacterial
  - Gonococcal
  - Mycobacterial
  - Virus
  - Lyme disease
- Crystal-induced
  - Gout
  - Pseudogout (CPPD)
  - Hydroxyapatite (acute calcific periarthritis)
- Hemarthrosis (hemophilia)
- Traumatic
- Septic bursitis (i.e. prepatellar bursitis)
- Flare of rheumatoid joint (existing RA)
- Psoriatic arthritis
- Reactive arthritis
- Osteomyelitis secondary to septic arthritis

## SELECTIVE GLOSSARY

**Poncet's disease**—In 1897, Poncet described polyarthritis in patients suffering from tuberculosis which was not caused by tuberculosis infection of the joints. It is characterized by polyarthritis that occurs during acute tuberculosis infection that affects persons with visceral or disseminated tuberculosis. No mycobacterial involvement can be found or other known cause of polyarthritis detected. Therefore Poncet's

disease remains a diagnosis of exclusion. Poncet's disease is postulated to be an immunologic reactive form of polyarthritis, and associated with an excellent prognosis with rapid resolution on commencing antituberculous therapy and no sequelae. Therefore, recognition of Poncet's disease can be important.

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## CHAPTER

# 6

## Back Pain

### SYNOPSIS

*Back pain* is one of the most common complaints and cause of disability in people seen in practice. More than 80% of the adults have had at least one episode of back pain, and many have had recurrent episodes since adolescence. Despite the frequency of low back syndrome, it is poorly understood and physical examination is often unrewarding in locating the etiopathogenesis of backache because low back pain may originate from many spinal structures, including ligaments, facet joints, the vertebral periosteum, the paravertebral musculature and fascia, blood vessels, the anulus fibrosus, and spinal nerve roots. Although advanced imaging tools such as CT, MRI, and nuclear scans have made it possible to distinguish wide variety of spinal ailments, their association between symptoms and imaging results is weak.<sup>1</sup>

Because of the high prevalence and high cost of dealing with this problem, and also because many experts believe the problem has been 'overmedicalized', resulting in rapidly rising workers' compensation claim burden being imposed on state budgets by low back pain (LBP) management, it is now clear, from the

findings of many extensive studies that, "uncomplicated acute LBP is a benign, self-limited condition that does not warrant any imaging studies. The vast majority of these patients are back to their usual activities within 30 days. The challenge for the clinician, therefore, is to distinguish that small segment within this large patient population that should be evaluated further because of suspicion of a more serious problem".<sup>2, 3</sup> The history and examination will identify both the majority of patients with self-limiting disease and also the minority who have a potentially serious conditions that may present as back pain needing further evaluation (Table 6.1). Diagnostic testing should not be a routine part of the initial evaluation, but used selectively based upon the history, examination, and initial treatment response.<sup>4</sup>

*Anatomically backache can be grouped as:*

- Upper back Pain (i.e. UBP or Thoracic or Dorsal Pain) related to the thoracic (T 1 to T 12) segments, and
- Low back pain (i.e. LBP or Lumbosacral Pain) related to the lumbosacral region (L 1-L5 + S1-S5), which may be associated with lower extremity symptoms.

**Table 6.1:** Potentially serious conditions that may present as back pain

Possible condition	Findings from the medical history
Fracture	<ul style="list-style-type: none"> <li>Serious accident or injury</li> <li>History of even a minor trauma or strenuous lifting in an older or osteoporotic patient</li> </ul>
Tumor or infection	<ul style="list-style-type: none"> <li>Chronic oral steroid use</li> <li>Age &gt;50 years or &lt;20 years</li> <li>History of cancer</li> <li>Constitutional symptoms (fever, chills, unexplained weight loss)</li> <li>Bacterial infection – TB, UTI</li> <li>Intravenous drug use</li> <li>Immunosuppression (corticosteroid use, transplant recipient, HIV infection)</li> <li>Pain worse at night or ‘rest pain’</li> <li>Failure to improve after 4 to 6 weeks of conservative low back pain therapy</li> </ul>
Cauda equina syndrome	<ul style="list-style-type: none"> <li>Saddle anesthesia</li> <li>Recent onset of bladder/bowel dysfunction</li> <li>Abnormal gait/severe or progressive neurologic deficit in lower extremity</li> </ul>
Referred pain	<ul style="list-style-type: none"> <li>Cardiac – Angina, MI</li> <li>Vascular – Pneumothorax, pulmonary embolism, dissecting aneurysm</li> </ul>

*Clinically backache is usually classified into:*

- Acute backache—Usually lasting <4 weeks of duration; mostly due to injury, strain, or faulty posture; symptoms such as pain, and restricted movements often confined to lower back, which are aggravated on coughing, straining, or bending. The main task is to watch on events, e.g. any neurological deficit, and address them as indicated.
- Chronic backache—Lasting >4 to 8 weeks of duration. At this point it is appropriate to reassess the patient’s symptoms and physical findings; perform selective investigations, evaluate *psychosocial barriers* (Table 6.2), and a surgical referral should be considered.

Since there is overlapping in the etiopathogenesis and management between the UBP, LBP, acute, and chronic disorders, their causes are considered together for the purpose of practical clinical approach.

## DIFFERENTIAL DIAGNOSIS

### Common

- Faulty posture
- Mechanical pain (muscle/ligamentous strain, sprain)

**Table 6.2:** Psychosocial barriers to back pain recovery

- Fear, financial problems, anger, or stress
- Depressed or negative moods, social withdrawal
- Overprotective family or lack of support
- Problems at work, e.g. heavy work, unsociable hours, low job satisfaction
- Belief that pain and activity are harmful
- “Sickness behaviors” such as extended rest
- Problems with claim and compensation

- Trauma/accident
- Infective (TB, i.e. Pott’s disease, epidural abscess, brucellosis)
- Lumbar spondylosis (degenerative OA)
- Spinal dysfunction (intervertebral disk prolapse, i.e. IVDP)
- Psychosocial (depression, anxiety, drug seeking behavior)
- Referred (lower cervical segments, renal calculi, pyelonephritis)
- Pelvis (in women—dysmenorrhea, pelvic inflammatory disease).

### Occasional

- Infective (osteomyelitis)
- Spinal abnormalities (kyphosis, scoliosis, secondary to poliomyelitis, Scheuermann’s disease)
- Vertebral collapse (osteoporosis, osteomalacia)
- Referred pain (cardiac—angina, MI; GI—duodenal ulcer, pancreas)
- Spondyloarthropathies (ankylosing spondylitis, Reiter’s syndrome)
- Malignancies (usually secondaries: from lungs, breast, prostate, thyroid).

### Rare

- Congenital (spina bifida, spondylolisthesis\*)
- Malignancies (primary: myeloma, Hodgkin’s)
- Referred pain (aorta, pulmonary embolism)

\* Spondylolisthesis, i.e. anteroposterior movement of one vertebral body upon another body or the sacrum, commonly L4 on L5, occasionally L5 on S1.

- Compensatory neurosis (legal issues, workers' compensation)
- Spinal canal stenosis
- Cauda equina syndrome
- Paget's disease
- Coccydynia
- Malingering.

## INVESTIGATIONS—GENERAL

### CBC, ESR, CRP

- Required when back pain is likely to be due to infection, inflammation, or malignancy.

### Urinalysis

- Including c/s may be indicated to rule out UTI and pyelonephritis as referred causes complicating low back pain.

### Spine X-ray

- Not useful in mechanical pain. Required if pain is associated with *red flags* (Table 6.3) indicating more serious problems.

**Table 6.3:** Lumbar spine X-rays should be limited to red flag indications

- Unrelenting night pain or pain at rest
- Fever above 38°C (100.4°F) for more than 48 hours
- Progressive neuromotor deficit
- Pain with distal numbness or leg weakness
- Loss of bowel or bladder control (retention or incontinence)
- Clinical suspicion of ankylosing spondylitis
- Significant trauma
- History of or suspicion of cancer
- Osteoporosis
- Chronic oral steroids
- Immunosuppressed or on immunosuppression medication
- Drug or alcohol abuse

*Note:* Generally AP and LAT X-rays are adequate; Oblique X-rays are not recommended; they add only minimal information in a small percentage of cases, and more than double the exposure to radiation (Ref. Table 6.4).

## INVESTIGATIONS—SPECIFIC

### Sr Calcium, Phosphorus, Alk Phosphatase, Acid Phosphate

- Elevated in malignancy, myeloma, and bony metastasis
- Serum acid phosphate is commonly elevated in prostate carcinoma with bone secondaries.

### Sr Uric Acid

- Elevated in gout and lymphoma
- Tophaceous gout may mimic epidural/extra epidural infection, abscess, or may coexist with other rheumatological disorders.

### PSA

- Backache may be an uncommon presentation of metastasized carcinoma of the prostate
- Prostate carcinomas with established malignant potential are more likely to be identified with PSA threshold >4.0 ng/ml.

### Plasmoprotein Electrophoresis

- Useful in the diagnosis of plasma cell neoplasms, e.g. multiple myeloma, and lymphoma.

### Bence Jones Protein

- May be raised in serum and/or urine in myeloma.

### CXR

- A solitary pulmonary nodule or metastatic deposits, usually from thyroid, or breast may be an associated lesion in elderly with chronic back pain.

### US Abdomen

- Intra-abdominal disorders such as aortic aneurysm, renal, and uterine disease are an occasional cause of referred pain to thoracic

or lumbar region which can be demonstrated on US of abdomen and pelvis.

### CT Spine

- CT scanning is considered the imaging modality of choice to evaluate patients for spinal trauma and vertebral fractures.

### HRCT Abdomen

- To confirm abdominal US findings, and /or for evidence of pancreatic, aortic, or pelvic lesions.

### MRI Spine

- MRI is noninvasive, does not involve radiation, covers a large area of the spine, and can show changes within the disk and vertebral body. It has become the imaging modality of choice in the diagnosis of radiculopathy, spinal cord abscesses, spinal cord tumors, spinal stenosis, and nontraumatic vascular lesions.

### Bone Scans (Technetium)

- In bone secondaries, and bone infection.

### Upper GI Endoscopy

- In patients suspected with GI causes, e.g. gastric or duodenal ulcer.

### CSF Analysis

- To confirm CNS infections—bacterial, tubercular, fungal, or viral.

### Electrodiagnosis

- Such as NCS, needle EMG evoke potential studies are usually not necessary in a clear-cut radiculopathy or in patients with isolated mechanical low back symptoms. These studies are helpful in the evaluation of patients with limb pain in whom the diagnosis remains unclear, e.g. peroneal neuropathy vs. radiculopathy and motor neuron disease.

**Table 6.4:** Limitations of X-rays in low back pain\*\*\*

- The radiation dose of one lumbar spine is equivalent to 150 chest X-rays and potential of gonadal irradiation.
- X-rays will not reveal a slipped disk.
- Even in well-established metastatic disease, the tumor must erode more than half of the vertebra before it is visible on plain X-ray.
- There is a high false-positive rate in lumbar spine.
- Several X-ray findings are of questionable clinical significance and may be unrelated to back pain. These findings include:
  - Disk calcification
  - Mild to moderate scoliosis
  - Single disk space narrowing
  - Spondylolysis
  - Lumbarization
  - Sacralization
  - Schmorl nodes
  - Spina bifida occulta

\*\*\* Diagnostic imaging practice guidelines for musculoskeletal complaints in adults - an evidence-based approach. Part 3: spinal disorders. Web site:

<http://www.guideline.gov/content.aspx?id=13009&search=adult+low+back+pain#Section405>

### Histocompatibility Antigen Test (HLA-B 27)

- In suspected spondyloarthropathies, e.g. ankylosing spondylitis.

### Myelography, Discography, Diagnostic Selective Nerve Blockade

- Myelography has been largely replaced by CT myelography or MRI.
- Discography and/or nerve blockade are indicated in selective chronic back pain patients in an attempt to either locate or abolish the exact source of back pain.

### Bone Marrow Biopsy/Aspiration

- In conditions undetectable by conventional methods, e.g. granulomatous bone disease, lymphomas, myelomas, and metastatic disease.

## CLINICAL NOTES

- A careful history taking and physical examination should address the following three aspects of back pain, which are mostly sufficient to arrive at a working diagnosis:
  - Is the back pain due to any systemic disease?

- Is there a neurological deficit that may entail surgical evaluation?
- Is there a psychosocial distress that is aggravating or prolonging the pain (see below)?
- The vast majority of LBP are mechanical, i.e. muscular and ligamentous strains. They are self-limiting and not severe
- Diagnostic testing should not be a part of their initial evaluation. However, a patient's failure to improve with conservative treatment (within 4–6 weeks) is an indication for further evaluation
- Absence of history of trauma does not exclude mechanical causes, IVDP, or vertebral fractures. A seemingly insignificant episode, such as a minor fall, may be a *red flag* for fracture in an elderly
- Examine the spine after its adequate exposure and in good light. Sometimes an unexpected finding such as midline mole, tuft of hair, dimpling, or hemangioma will spot the diagnosis of spina bifida occulta
- Palpation is an important component of examination. Unlike the lumbar spine, the thoracic vertebrae are superficial and it is relatively easy to locate affected (painful) segment
- *Sciatica* usually involves L4 - L5, L5- S1 nerve roots, either alone or together (Table 6.5)
- IVDP is very uncommon in the thoracic spine
- Thoracic spine pain is frequently associated with the lower cervical spine lesions
- The thoracic spine is the commonest site in the vertebral column for metastatic deposits
- Back pain that is *unilateral* may have a urologic etiology such as pyelonephritis, or obstructive nephropathy
- Only congenital abnormalities which may cause back pain are spina bifida and spondylolisthesis. Sacralization<sup>†</sup> of L5 is generally asymptomatic
- The pain of myocardial ischemia, from angina, or myocardial infarction can be referred to the interscapular region of the thoracic spine. A clinical rule is to consider the cause of thoracic pain as cardiac until the examination and investigations prove otherwise
- Beware of herpes zoster in the thoracic segments especially in old and immunocompromised persons
- Beware of spinal canal stenosis, especially in middle-aged or elderly patient, with history of *neurogenic claudication*<sup>‡</sup> such as back pain referred to hips, paresthesias worsened by back extension, walking and relieved by sitting, or lying with the trunk flexed (finds hills easier to climb than to descend)
- In chronic cases, exclude significant pathology. Focus on counseling; discussing preventive measures and patient education for self-management of future episodes improves prognosis. Avoid unnecessary, costly investigations
- Suspect malingering, especially in patients with legal, or mediclaim issues. False-positive physical findings such as positive SLR tests may be seen, yet the person may not have any problem while walking, sitting, or climbing. However, when the diagnosis of malingering is doubtful, it is safest to assume a person is not, unless a contradictory symptom or sign is witnessed (Table 6.6)<sup>5</sup>
- Although any one episode of back pain may be started by a physical problem in the back, its prognosis is vastly influenced by psychosocial factors. The added morbidity of depression and anxiety with chronic pain is strongly associated with more severe pain, greater disability, and poorer health-related quality of life.<sup>6</sup>

### RED FLAGS

- Back pain associated with severe or progressive neurological deficit is a medical emergency; suspect IVDP, cord compression,

<sup>†</sup> Sacralization—fusion of the sacrum and L5 vertebra.

<sup>‡</sup>Neurogenic claudication, i.e. presence of neurological symptoms/deficit in lower extremities while walking with normal peripheral pulses.



**Table 6.5:** Sciatica — Nerve root compression and symptoms

Level/ disk location	Nerve root involved	Pain radiation	Neurological deficit	Sciatica
L3 – L4	L4	Lateral thigh and inner aspect of leg	Patellar jerk(reflex); dorsiflexion of foot (motor)	Uncommon
L4 – L5	L5	Anterolateral leg and great toe	Extensor of great toe (motor)	Common
L5 – L6	S1	Posterior leg and lateral toes	Ankle jerk (reflex); plantar flexion (motor)	Common
Midline disk hernia -tion	Cauda equina	Bilateral leg weakness	Saddle anesthesia urinary retention	Uncommon

**Table 6.6:** What physical exam techniques are useful to detect malingering?

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines malingering as:

*“The intentional production of false or grossly exaggerated physical or psychological symptoms motivated by external incentives such as avoiding military duty, avoiding work, obtaining financial compensation, evading criminal prosecution, or obtaining drugs.”*

Malingering is not considered a mental disorder because symptoms are intentionally produced for external incentives.

Several exam tests are commonly thought to detect nonorganic causes of low back pain such as Waddell's signs, Mankopf's test, Hoover's test, Arm Drop test, Midline Split test, etc. which have low diagnostic yield.

Since no examination technique objectively proves malingering, the DSM-IV recommends suspicion of malingering for patients who present with 2 or more of the following:

- Medicolegal issues
- Disagreement between objective and subjective stress or disability
- Noncompliance with evaluation or treatment, or
- Antisocial personality disorder.

vertebral fracture, and viral myelitis (herpes, polio, HIV). Hospitalization is indicated.

- In a patient with acute back pain, who is withering with pain and clinically unstable, suspect intra-abdominal or vascular process. Hospitalization is indicated.

- Cauda equina syndrome—Back pain with bladder or bowel incontinence, saddle area perineal numbness, disturbed gait is an emergent condition.
- Beware of patients, especially elderly, with weight loss, pain at rest, or constant pain at night; significant pathology, especially malignancy, must be ruled out.
- In elderly men, especially over age 50 with back pain, per rectal examination is mandatory; associated PSA estimation may be indicated to rule out prostate malignancy.
- Chronic back pain before the age of 20 years is an indication to rule out primary spinal tumors, e.g. osteosarcoma.

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## CHAPTER

# 7

## Breast Lump

### SYNOPSIS

A *breast lump*\* is a swelling or a protuberance in the breast which feel different from surrounding breast tissue.

Although breast lumps may appear at all ages—infants, young girls, and teenage boys—they are transitory and disappear on their own over a period of months. It is the breast lump in an adult woman that raises concern for breast cancer, even though most lumps turn out to be benign breast lesions.

Frequently, it is the patient who has noticed the 'lump' herself and expects reassurance or early evaluation. Not infrequently, a lump may have been detected on routine mammographic screening<sup>†</sup> called as a 'mammographic lesion'<sup>‡</sup>.

\*The terms breast 'lump' and breast 'mass' are used interchangeably; however, since the term 'mass' is also used in the context of breast imaging modalities, the term 'lump' may be preferred to avoid confusion.

<sup>†</sup>'Screening' is performed in the absence of symptoms; when symptoms exist, the evaluation may dictate going beyond screening procedures.

<sup>‡</sup>Screening mammographic 'lesion' could be a lump, architectural distortion, asymmetric parenchyma, calcification, or skin changes. These findings are further defined by diagnostic mammographic imaging modalities as benign or malignant as per the Breast Imaging-Reporting and Data System protocol.

In either case, however, the importance of correctly diagnosing a breast lump early can not be understated irrespective of woman's age, clinical status, and risk factors. Goodson WH et al states, "The leading cause of physician delay in diagnosis of breast cancer continues to be inappropriate reassurance that a mass is benign without biopsy. Reducing delay in diagnosis will require less willingness to rely on clinical examination to decide that a mass is benign, less reliance on benign mammography reports to decide not to biopsy a mass, and a requirement that fine-needle aspiration biopsy be done by persons with demonstrated competence for the procedure".<sup>1</sup>

As most women who present with breast lump are emotionally distressed, the goal of the evaluation is not only differentiating a benign breast disease from cancer, but also addressing the patient's symptoms and alleviating the anxiety about breast cancer.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Benign breast disorders (fibrocystic condition, fibroadenoma)



- Breast abscess (mastitis — acute or chronic)
- Breast cancer.

### Occasional

- Lipoma, pseudolipoma<sup>§</sup>
- Cysts (galactocele, solitary cyst, multiple cysts, sebaceous cyst)
- Drug induced (aldactone, aldomet, and digitalis).

### Rare

- Injuries of the breast (traumatic fat necrosis, hematoma)
- Tuberculous abscess
- Retromammary abscess (cold abscess)
- Phyllodes tumor
- Metastasis (carcinoma of bronchus, thyroid, opposite breast).

## INVESTIGATIONS—GENERAL

### CBC

- Anemia in chronic infection and malignancy; leukocytosis in breast abscess.

### ESR

- Elevated in infection, tuberculosis and malignancy.

### LFTs

- Elevated liver enzymes with secondary deposits in liver.

### Serum Calcium

- Elevated in secondary deposits in bones.

### CXR

- To detect underlying lung disease, e.g. TB, secondary deposits in lungs and ribs.

<sup>§</sup>'Pseudolipoma' is a bunching of fat between retracted suspensory ligaments of the breast and is associated with an underlying carcinoma.

## INVESTIGATIONS—SPECIFIC

### Mammography

- Indicated as an initial screening procedure to evaluate a breast lump in women aged 30 years and more. The purpose is to evaluate a palpable or *dominant*\*\* mass, or to define the presence or absence and extent of nonpalpable *lesion* associated with the mass; and also to identify additional abnormalities in the ipsilateral or contralateral breast that may influence further management. The purpose of the mammogram is *not* to diagnose the palpable findings, and normal mammogram does not ensure absence of malignancy
- Because the breasts are relatively radiodense in women under 30 years of age, mammography is rarely of value in this age group. In older women some amount of fatty displacement of breast tissue makes mammographic evaluation more informative
- Mammographic findings that suggest malignancy include increased density, irregular margin, speculation, and clustered irregular microcalcifications.

### Digital Mammography

- This procedure greatly facilitates the use of computer-aided-detection (CAD), which allows further evaluation of an abnormal mass or some breast lesion that may have missed on initial evaluation. CAD is used selectively especially in women with a genetic predisposition for breast cancer, where intensified early detection programs may have to start from 25 to 30 years of age.<sup>2</sup>

\*\**Dominant* mass is a palpable mass which persist throughout the menstrual cycle. These masses may be discrete or poorly defined, but they differ in character from the surrounding breast tissue and the corresponding area in the contralateral breast.

### FNAC or FNA Biopsy (FNAB)<sup>††</sup>

- The material aspirated, either fluid from the cyst or samples of solid lesions, are subjected to cytological examination. Any finding that is suspicious for malignancy on FNA is subjected to surgical excision for definitive diagnosis
- This procedure can be combined with US, i.e. US guided FNAC, to further assess poorly defined palpable masses
- If FNA is done *before* mammography, the diagnostic mammography should be delayed for 2 weeks after needle aspiration so as to avoid false-positive results due to trauma and possible hematoma formation.

### US Breast

- Indicated as an initial procedure to evaluate palpable masses in women under 30 and lactating or pregnant women
- Helps to differentiate a benign simple cyst, a complex cyst, or any suspicious mammographic solid density
- Useful for guidance of interventional procedures
- Not indicated as a screening study for occult masses.

### US Abdomen

- To detect metastasis, especially to liver.

### MRI

- It has high sensitivity for breast cancer besides aiding in its (TNM) staging and management. MRI is also found to be an optimum method of imaging breast implants and detecting implant leakage and rupture.

<sup>††</sup>Some distinction is made between FNAC and FNAB; FNAC refers to aspiration of *fluid* for cytology, and FNAB refers to obtaining tissue from *solid* lesion for cytological evaluation.

*Screening MRI* may be helpful for women for whom mammography is not optimal, such as young women at substantially increased risk for breast cancer because of known *BRCA1* or *BRCA2* mutations.<sup>3</sup>

### Core-needle Biopsy

- Mostly used to evaluate small or difficult-to-palpate lesions, or nonpalpable breast masses identified on mammogram with ultrasound guidance. A minimum of four core samples are taken to achieve greater histologic accuracy.

### Excision Biopsy

- Indicated if FNAC or core Biopsy is inconclusive and there is clinical suspicion of malignancy; the other possible indications are: a discrete lump which is increasing in size, and when the patient is not willing to 'wait-on-events' and anxious to have a rapid diagnosis.

### Triple Diagnosis Test

- It's a combination of clinical breast examination (CBE), imaging studies, and FNAC, used as an alternative to surgical excision to establish that the breast mass is benign.
- If the above three parameters indicate a benign process, the breast mass is considered as benign. If biopsy is deferred after triple diagnosis, careful follow-up is warranted. If any of these three modalities suggests malignancy, excisional biopsy is mandatory.

### Genetic Testing for Breast Cancer<sup>4</sup>

- Woman with personal history of breast cancer at young age; family history of breast cancer in two or more close relatives, such as parents, siblings and children; a family history of breast cancer in more than one

generation; a family member who has both breast and ovarian cancers; a male relative with breast cancer; or a positive BRCA1 or BRCA2 genetic test in a relative; may undertake genetic testing after proper genetic counselling to see if she actually do have a mutated gene. If a woman has mutations in either of two breast cancer susceptibility genes (BRCA1 and BRCA2), her risk of breast or ovarian cancer is significantly higher than that of a woman without such a mutation.<sup>##</sup>

## CLINICAL NOTES

- History—Important components of the history are listed in the Table 7.1.

**Table 7.1:** Breast lump—medical history

<ul style="list-style-type: none"> <li>Age of menarche</li> <li>Details of menstrual history</li> <li>Breast changes or symptoms noted with menstrual period</li> <li>Age at first pregnancy</li> <li>Number of pregnancies and deliveries</li> <li>Nipple discharge (frequency, color, unilateral, or bilateral discharge)</li> <li>Age of menopause</li> <li>Any exposure to hormone therapy or oral contraceptive pills (age when began, duration, dosage)</li> <li>Previous breast biopsies and their corresponding diagnosis</li> <li>Family history of breast cancer (including in relatives), and other carcinomas, e.g. ovarian</li> </ul>
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- Breast lump—Duration of the mass; how and when it was first noticed; change in its size, shape, and consistency; its relation to menses; changes in surrounding skin; and trauma should be questioned.
- Presence of risk factors (Table 7.2) indicates highest risk for breast carcinoma.

**Table 7.2:** Risk factors for breast cancer

<ul style="list-style-type: none"> <li>Early menarche, before age 12</li> <li>Age greater than 50 years</li> <li>Late menopause, after age 50</li> <li>Age greater than 30 at first birth</li> <li>Nulliparity</li> <li>Ionizing radiation exposure</li> <li>Family history in first degree relative (i.e. mother, sister, daughter)</li> <li>Previous history of breast cancer, breast biopsy showing atypical hyperplasia</li> <li>Minor risk factors include: alcohol intake, obesity (BMI <math>\geq 30</math> kg per m<sup>2</sup>), high economic status, HRT, and use of oral contraceptive pills</li> </ul>
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- Breast pain (mastalgia), breast lump, and nipple-discharge are the most common symptoms
- The most common causes of breast pain are fibrocystic disease, i.e. cyclical mastalgia (pain increases before the menstrual period and settles afterwards), and mastitis
- A breast lump in a woman in the ages of 15 and 25 years suggests fibrocystic condition, or fibroadenoma; cysts tend to occur commonly and frequently around the fourth decade of life and in the perimenopausal period. In any woman with breast lump, no matter what her age, the probability of developing breast cancer increases throughout life
- Nipple discharge—Important features to be evaluated by history and physical examination include:
  - Nature of discharge
  - Association with a mass
  - Unilateral or bilateral
  - Spontaneous or manually expressed
  - Relation to menses
  - Premenopausal or postmenopausal
  - Any exposure to hormones or contraceptive pills.
- Characteristics of discharge—May be physiological (pregnancy or lactation, i.e. galactorrhea). Purulent discharge may be caused by mastitis, breast abscess, or duct

<sup>##</sup>FDA has approved the *TOP2A* FISH pharmDx device to test for the *TOP2A* (topoisomerase 2 alpha) gene in cancer patients. Web site - <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01774.html>

ectasia; unilateral blood stained discharge increases the concern for malignancy; spontaneous persistent discharge may indicate hyper-prolactinemia and warrants endocrine work-up

- Skin changes overlying the lump such as orange peel appearance, retraction, inversion, and ulceration of the nipple strongly indicate breast cancer
- CBE of the breast lump is done in at least two positions: Sitting (i.e. upright) and supine with the woman's arms behind her head. Although CBE can detect a variety of abnormalities, by far the most common are those detected by palpation. The entire breast tissue, i.e. the four quadrants, is palpated gently, systematically and individually, including the tail of Spence, by applying varying pressure. This is clinically significant because abnormalities can arise in the 'tail' region (e.g. axillary extension of ipsilateral breast cancer) just as they can in other areas of the breast
- Normal breast tissue is dense, firm, and elastic. Generalized nodularity and tenderness is common during the menstrual cycle. It is important to differentiate between a dominant lump and areas of nodularity which can occur at any age
- A dominant mass or lump is distinct from surrounding tissues, asymmetrical relative to the other breast, and persist throughout a menstrual cycle
- In a premenopausal woman, CBE is ideally performed 3 to 10 days after the onset of menstruation (when ovarian hormones exert least influences; breast engorgement and nodular structure of breast tissue is usually decreased)
- Examination of the regional lymph nodes, i.e. axillary, cervical, and supraclavicular, for their site, size, and associated features such

as pain, tenderness, and consistency is a critical component of the examination

- Any breast lump must be evaluated to determine whether it is cystic or solid; neither the CBE nor mammography can make this distinction
- Although benign masses are often mobile, soft, or cystic, these features are not specific enough to exclude malignancy
- Malignant breast lump—Common symptoms include:
  - Often painless, possibly increasing discomfort, especially prior to menstruation.
  - Changes in the breast that include distortion, puckering of the skin and nipple retraction.
  - Lump that may be firm or hard with varying degree of fixity to surrounding tissues, overlying skin, or underlying pectoral muscles.
  - Malignant ulcer may be present, and the nipple discharge is usually bloody.
- Symptoms suggestive of metastasis disease are—bone pain, back pain, cough, dyspnea, headache, personality changes, seizures, and abdominal symptoms and jaundice
- If the CBE yields findings suspicious of carcinoma, the American Joint Committee on Cancer (AJCC)<sup>5</sup> clinical staging should be included in the medical records.

## RED FLAGS

- Never ignore a women's insistence that an area of her breast is different or has changed
- An asymptomatic breast mass is the most common presentation of the breast cancer
- Any eczematous rash appearing on the nipple or areola indicates underlying breast malignancy
- A negative mammogram does not replace the need for biopsy of the palpable mass

- Tuberculosis of the breast, though an uncommon disease, is still present and is also misdiagnosed with carcinoma or bacterial abscesses. Moreover, simultaneous occurrence of these two major illnesses in the breast, i.e. tuberculosis and carcinoma has been reported in the literature which can lead to many problems regarding diagnosis and treatment.<sup>6,7</sup>

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## CHAPTER

# 8

## Chest Pain

### SYNOPSIS

*Chest pain*—broadly defined as any discomfort in the anterior thorax occurring above the epigastrium and below the mandible—can be one of the most challenging problem managed by the physicians. The typical patients' concern with the first bout of chest pain is their apprehension of the onset of cardiac pathology, such as CAD. However, of the patients' referred to the Rapid Access Chest Pain Clinic, 52% did not have cardiac chest pain.<sup>1</sup> In another study statistics show that more than 50% of patients referred to cardiologists for chest pain are ultimately found to have noncardiac chest pain; that is, their chest pain is not shown to be caused by cardiac ischemia.<sup>2</sup> Further, patients with chest pain who present for the first time to ambulatory care or to the emergency room, only 11 to 39% are ultimately diagnosed with coronary artery disease.<sup>3</sup> The balance of patients (approx. 50–60%) experience *noncardiac chest pain*.<sup>4</sup> Thus, although for the patient with chest pain, the possible underlying (notably cardiac) cause is the chief concern, for the physician, the cause, cardiac or otherwise, is often unrelated to the complaint of chest pain.

When a person complains of chest pain as 'crushing, retrosternal pain, or substernal pressure', it usually suggests a cardiac source of chest pain. However, only 50% of patients with acute coronary syndrome (ACS) describe their pain in classic terms such as crushing or pressure-like; it is often experienced more as a 'nonspecific' sensation of discomfort than actual pain. Many other descriptive terms are also used to convey chest pain, such as dull, aching, tightness, squeezing, soreness, burning, or 'gas'. Diabetic and elderly people who may have cardiac pain are more likely not to experience chest pain, or to have nonspecific symptoms such as dyspnea, nausea and vomiting, unusual fatigue, or syncopal attacks. Moreover, in women, the presentation of chest pain of cardiac origin is frequently atypical than in men. Therefore, the physician has to be aware of both the typical and atypical presentations of chest pain, especially of cardiovascular origin.

The differential diagnosis of chest pain includes conditions affecting organs throughout the thorax, neck, jaw, shoulder, arm, forearm, and upper abdominal viscera (i.e. the area covered by six dermatome — T1 to T6 – sensory nerves), with prognostic implications that vary



from benign to life-threatening, including death. Nora Goldschlager, MD, Professor of Medicine, University of California, San Francisco states, “evaluation of chest pain is really all about not missing CAD\*, and in particular not missing things that could be ACS†, and calling them something else and sending the patient home”.<sup>5-8</sup>

The extent of evaluation of the chest pain is chiefly determined by the patient’s age, family history, cardiac risk factors’ estimation, total ischemic burden, and cost-effective analysis of noninvasive and invasive procedures, so that unnecessary tests, procedures, anxiety, and hospitalization are minimized or avoided. However, chest pain is not always of cardiac origin. In some patients, further workup may reveal a noncardiac cause of chest pain, while in others, the results may be inconclusive. It is in this latter population that diagnosis can be particularly challenging. Despite test results that are negative for CAD, they may still have cardiac or systemic diseases.<sup>9</sup>

## DIFFERENTIAL DIAGNOSIS

### Common

#### Cardiac

- Stable effort angina
- Unstable angina pectoris
- Coronary spasm (Prinzmetal’s angina)
- MI (ST-elevation, and non ST-elevation MI)
- Cardiac arrhythmias.

\*Coronary artery disease (CAD) may manifest as: stable angina; unstable angina, non-Q wave MI (NQMI), non-ST segment elevation MI (NSTEMI); ST segment elevation MI (STEMI); heart failure; sudden death; and as an incidental finding (asymptomatic).

†The term acute coronary syndrome (ACS) refers to a range of acute myocardial ischemic states. It encompasses unstable angina, non-ST segment elevation myocardial infarction (ST segment elevation generally absent), and ST segment elevation infarction (persistent ST segment elevation usually present). — BMJ 2003; 326:1259-61.

#### Gastrointestinal

- GERD
- Functional GI disease
- Peptic ulcer disease
- Gallstones
- Pancreatitis.

#### Musculoskeletal

- Chest wall syndrome (painful rib syndrome, slipping rib syndrome)
- Chest wall bruising or trauma
- Costochondritis (Tietze’s syndrome)
- Cervical/thoracic radiculopathy.

#### Pulmonary

- Bronchitis
- Pneumonia
- Pleural effusion(due to CHF, TB, malignancy).

#### Emotional/Psychiatric

- Panic/anxiety
- Depression
- Somatization
- DaCosta syndrome
- Fibromyalgia.

### Occasional

- Pericarditis (due to rheumatic fever, TB)
- Pulmonary embolism(PE)
- Aortic stenosis
- Intercostals neuritis (herpes zoster: prior to the eruption; diabetes mellitus).

### Rare

- Diffuse esophageal spasm
- Cardiac syndrome X (CSX — microvascular angina: *vide infra* ↓↓)
- Cardiac causalgia<sup>#</sup>
- Hypertrophic cardiomyopathy

<sup>#</sup>Pain with tenderness of anterior thoracic wall, burning in nature, observed mostly in post CABG patients.



- Aortic dissection
- Mitral valve prolapse (MVP)
- Pulmonary hypertension (PH)
- Pneumothorax.

## INVESTIGATIONS—GENERAL

### CBC

- Anemia — aggravates cardiac ischemia.
- Leukocytosis in lung infection, infarction, and bacterial pericarditis.

### Blood Glucose/Lipid Profile

- To assess risk factors for CAD.

### ECG

- When obvious ST-segment elevation is present in patients with acute chest pain, the diagnosis of myocardial injury is straight forward. However, significantly more than 50% of patients with AMI have nondiagnostic ECG changes. The ECG becomes even less sensitive with increasing age and in those with a previous MI. Also, many ECG patterns interfere with the diagnosis of AMI. These include left bundle-branch block, WPW syndrome, early repolarization ST changes, left ventricular hypertrophy, hyperkalemia, digoxin effect, etc
- Further, ST-T changes in patients with chest pain due to MI, PE, and pericarditis can be similar; therefore, the clinical history and physical examination, as well as ECG clues, must be considered before making a diagnosis
- As patients with initially normal ECG are still at risk for life-threatening complications and death, it is important to obtain serial ECGs for any evaluation.

### CXR

- PA projection provides valuable information about pneumonia, pneumothorax, mediastinal disease, pulmonary hypertension, aortic dissection, spine disease and trauma

- Dilatation of individual cardiac chambers and cardiomegaly is seen in hypertension, valvular heart disease and chronic CHF.

### Cardiac Enzymes

- Levels of creatine kinase MB isoenzyme (CK-MB) usually rise above the normal range within 4 hours after the onset of myocardial infarction, and serial sampling of CK-MB over a period of 12 to 24 hours permits the detection of virtually all acute myocardial infarctions. However, CK-MB elevations can result from causes other than myocardial injury
- The cardiac troponin T and I markers are more specific than CK-MB for myocardial injury. After myocardial injury, the levels of cardiac troponins rise after approximately the same amount of time as CK-MB levels and remain elevated for up to 2 week; therefore, they are not useful in detecting episodes of reinfarction. However, the assay for CK-MB permits the detection of reinfarction
- The most appropriate strategy followed at many hospitals is the combined use of the CK-MB and Troponin I and T
- Although troponin has greater specificity than myoglobin and CPK-MB for myocardial damage, elevated levels may be present in patients with nonischemic heart disease or noncardiac disease. Cardiac causes, such as heart failure, myocarditis, and the use of cardiotoxic drugs, such as doxorubicin, 5-fluorouracil, and trastuzumab can produce nonischemic troponin elevations. Noncardiac causes, such as pulmonary embolism, sepsis, high-dose chemotherapy, stroke, subarachnoid hemorrhage, pre-eclampsia, and renal failure can also produce such elevations. Therefore, elevated troponin levels do not invariably signify myocardial damage.

## INVESTIGATIONS—SPECIFIC

### Exercise ECG

- The overall sensitivity and specificity is about 50–70% in patients with CAD. The ECG is monitored for ST-depression and any ventricular arrhythmias. The patient is also monitored for any fall in blood pressure, or complaints of chest discomfort, or dyspnea. The test is performed if diagnosis is in doubt, for prognostic reasons, or to aid in the timing of additional investigations, e.g. Coronary angiography. A normal stress ECG does not rule out CAD; both false-positive and false-negative results are common.

### Echocardiography – 2-D and Doppler<sup>10</sup>

- In patients with acute chest pain due to MI, this technique can be performed at the bedside, and is very useful for assessing right and left ventricular function, wall motion abnormalities, identification of vegetations in endocarditis, and for detecting important complications such as mitral regurgitation, ventricular septal defects, pericardial effusion, and cardiac rupture.
- In aortic dissection, Doppler echo may show aortic regurgitation, a dilated aortic root and, occasionally, the flap of the dissection.
- In patients presenting with atypical chest pain, suspected to be due to MVP, 2-D cardiac echo findings of >2 mm superior displacement of the mitral leaflets into the left atrium during systole, with a leaflet thickness of at least 5 mm can be diagnostic.

### HRCT/MRI

- Particularly useful in imaging the aorta in suspected aortic dissection
- HRCT with contrast has been shown to have sensitivity and specificity comparable to that of contrast pulmonary angiography,

and in recent years, HRCT has been accepted both as the preferred primary diagnostic modality, and also as the criterion standard for making or excluding the diagnosis of pulmonary embolism.

### Ventilation-perfusion (V/Q) Scans

- V/Q scan remains an important part of the evaluation for detecting pulmonary thromboembolism when HRCT angiography is not available.

### Myocardial Perfusion Imaging

- Intravenous administration of a radioisotope (e.g. <sup>201</sup>thallium or tetrafosmin) at rest and during stress provides additional information about myocardial perfusion. Areas of decreased uptake during exercise, followed by normal uptake at rest suggest ischemia; whereas areas of persistent defect indicate infarction.

### Coronary Angiography

- This technique, which delineates coronary artery anatomy, is the gold standard and indicated in those patients who are at high risk for CAD by noninvasive tests, and for those with persistent symptoms despite medical therapy, i.e. medical vs. surgical management, including stenting and CABG.

### Intravascular Ultrasound (IVUS)

- Coronary angiography, although generally accepted to be the gold standard of diagnosis, is not 100% sensitive for exclusion of coronary artery disease. Coronary angiography detects the *later stage* of atherosclerosis (negative remodeling stage), when larger plaques significantly impinge on the coronary lumen. Angiography may fail to detect the *early stage* of atherosclerosis (positive remodeling stage), when smaller plaques cause minimal or no

luminal impingement. This stage is detectable only by intravascular coronary ultrasonography.<sup>11</sup>

### **Multislice Computed Tomography (MSCT)/64-Slice Spiral Computed Tomography**

- Multislice computed tomography coronary angiography (MSCT-CA) has emerged as a powerful noninvasive diagnostic modality to visualize the coronary arteries and to detect significant coronary stenoses. The latest generation 64-slice computed tomography (CT) scanners are a robust technique which allows high-resolution, isotropic, nearly motion-free coronary imaging. Coronary stenoses are detected with high sensitivity and a normal scan accurately rules out the presence of a coronary stenosis. With the introduction of further novel concepts in CT-technology one may expect that MSCT-CA will become a clinically used diagnostic tool.<sup>12</sup>

### **GI Studies**

- Common GI causes of acute noncardiac chest pain include esophageal spasm, reflux esophagitis, peptic ulcer, pancreatitis, cholecystitis, and esophageal perforation. According to one study, GI disease is the most common cause for which patients are admitted to a coronary care unit to have MI ruled out, accounting for 42% of all cases of chest pain.<sup>13</sup>
- Esophagogastroduodenoscopy, 3 hours monitoring of esophageal pH, esophageal manometry, Bernstein test, and ultrasonic examination of the abdomen may be indicated where symptoms are atypical, or cardiac evaluation is normal.

### **PFTs**

- Can be helpful in patients with pulmonary chest pain, in differentiating obstructive vs. restrictive disease and its severity.

### **TFTs**

- Both hyper- and hypothyroidism can precipitate CAD. Low or undetectable TSH in hyperthyroidism may contribute to anxiety associated chest pain.

### **CLINICAL NOTES**

- Regardless of where care is given – primary or emergency department—the critical first step in managing patients with chest pain is to explore the possibility of potentially life-threatening causes of the symptoms, including ACS, aortic dissection, and PE
- A focussed, expeditiously performed physical examination should include: heart rate, palpation of peripheral pulses, BP measurement in both arms, and estimation of oxygen saturation. Other salient features are listed in Table 8.1. Besides coronary risk factors' stratification, few key investigations to search for evidence of CAD (a 12-lead ECG, CXR, and serial measurements of cardiac enzymes) may be indicated in patients with acute undifferentiated chest pain
- Physical examination usually does not reveal any abnormality in the diagnosis of aortic dissection and PE; thus clinical suspicion must be heightened in order to diagnose these conditions
- If acute CAD seems unlikely to be the cause of the chest pain, the possibility of pulmonary, GI, and musculoskeletal conditions, as well as pericarditis and other cardiovascular causes (e.g. cardiomyopathy, CSX) should be investigated
- For clinical evaluation, patients with chest pain can be classified into three broad groups, namely: acute pain of recent onset; recurrent pain – lasting for minutes; and persistent pain – lasting for hours or even days (Table 8.2).

**Table 8.1:** Physical findings in acute chest pain

Features	Cause
Altered mental state; cold extremities; pulsus alternans; tachycardia; hypotension; $S_4$	Low cardiac output: MI; LVF
Dyspnea; tachycardia; hypoxia; elevated JVP; rales; $S_3$ gallop	Acute pulmonary edema: MI; LVF
Pulse deficit; hypertension; BP difference between two arms; murmur of aortic insufficiency; neurological deficit	Aortic dissection
Tachypnea; hypotension; elevated JVP; right ventricular lift; accentuated $P_2$ ; pulmonary rales, consolidation, effusion	Pulmonary embolism
Dyspnea, dysphagia, hypoxia; elevated JVP; hypotension; tachycardia; pulses paradoxus; muffled heart sounds; pericardial rub	Cardiac tamponade
Dyspnea; hypoxia; tachycardia; mediastinal shift; hyperresonance; absent/diminished breath sounds; subcutaneous emphysema	Pneumothorax
Hamman's sign (crunching, rasping sound, synchronous with heartbeat)	Pneumomediastinum; Pneumopericardium; esophageal rupture

**Table 8.2:** Classification and examples of chest pain based on duration

Duration	Examples
Acute chest pain—lasting for few seconds to few minutes	Cardiac: ACS; HCM; aortic stenosis; pericarditis Vascular: Aortic dissection; PE; PH Pulmonary: pneumonia; tracheobronchitis; pleuritis; pneumothorax; mass lesion GI: GERD; PUD; biliary disease; pancreatitis Musculoskeletal: costochondritis; cervical disk Lesion; trauma Others: breast disorders; herpes zoster; anxiety; emotional
Recurrent chest pain – lasting for minutes	Cardiac: (same as in above) vascular: PE; PH pulmonary: (same as in above, except pneumothorax) GI / musculoskeletal, and others: (same as in above)
Persistent – lasting for hours and days together	Cardiac: pericarditis Pulmonary: ( same as in above, except pneumothorax) GI / musculoskeletal, and others: (same as in above)

- Careful assessment of patient's history and cardiac risk factors is often the most helpful starting point. Historical features generally useful in the diagnosis of cardiac origin of chest pain include:

- Location (diffuse, anterior retrosternal pain, chest pain, interscapular pain)
- Radiation (to the neck, jaw, shoulders or arms)
- Aggravating factors (exertion, meals, cold weather, and stress)
- Duration (brief pain lasting few seconds to few minutes)
- Relieving factors (rest)
- Associated symptoms (dyspnea, cough, diaphoresis, presyncope, syncope).
- Common features of *atypical* chest pain are listed in Table 8.3
- Coronary risk factors include—Age, family history of heart problems, diabetes, hypercholesterolemia, smoking, hypertension, obesity, sedentary lifestyle, and stress or competitive occupation
- Although cardiac risk factors are common in patients with ACS, they are not a prerequisite; absence of such risk factors does not lower the risk of ACS<sup>14</sup>
- The key distinctive point in the clinical diagnosis of chest pain caused by CAD is in its relation to physical exertion. If the chest discomfort is not precipitated by physical exertion, it is highly unlikely that coronary artery disease of any significant degree is present (Table 8.4)
- Occasionally, effort-induced ischemic pain disappears while the activity continues; this is known as *walkthrough* or *second wind* angina
- Occasionally, diagnosis based solely on history may not be possible; e.g. descriptions of chest pain of cardiac, upper gastrointestinal, or gallbladder origin can be identical. Hence, although patient's history is usually a valuable starting point, it may not provide a definite diagnosis because of their poor specificity in diagnosis of chest pain<sup>15</sup>
- Symptoms of *angina equivalents*, i.e. cardiac ischemia without chest pain, such as

**Table 8.3:** Symptoms of atypical chest pain

- Features suggesting atypical, also called as non-cardiac/ nonanginal pain includes:
- Pain—dull ache, sharp, shooting, 'knife-like', pleuritic, pain brought on by respiratory movements or cough.
- Location—pain localized with one finger, left sub-mammary.
- Aggravating factors – body movements, respiration, swallowing, palpation of chest.
- Duration – brief episodes lasting a few seconds, or constant lasting for days.

**Table 8.4:** Questions to differentiate patients with non-cardiac chest pain from those with coronary heart disease<sup>#</sup>

Question	Response	
	Typical	Atypical
If you go up a hill (or other stressor) on 10 separate occasions on how many do you get the pain?	10/10	<10/10
Of 10 pains in a row, how many occur at rest?	<2/10	≥2/10
How many minutes does the pain usually last?	<5	≥5

When answers to all three questions are "atypical" the chance of coronary disease is only 2% in patients aged <55 years and 12% in those aged ≥55

<sup>#</sup>Christopher Bass et al. Clinical review ABC of psychological medicine chest pain. *BMJ* 2002; 325:588-91.

breathlessness; profound, unexplained, sudden-onset fatigue, especially in the elderly and diabetic patients is common

- Pain that radiates to the left arm and shoulder is often assumed to indicate coronary ischemia, whereas pain that radiates to the right shoulder is thought to suggest a biliary source. However, chest pain that radiates to the right shoulder is more specific for pain of cardiac origin than pain that radiates to the left shoulder. Radiation of chest discomfort to the right arm is also consistent with the diagnosis of acute IHD<sup>16</sup>
- Acute, sudden and severe chest pain described as ripping or tearing that is maximal at onset and radiates to interscapular area raises the possibility of aortic dissection. Important diagnostic feature is the inequality in the pulses, e.g. carotid, radial and femoral, and a blood pressure differential of greater than 20 mm Hg

- The pain of diffuse esophageal spasm may mimic that of angina pectoris, including that the relief in many cases is obtained with nitroglycerine
- Severe chest pain, retrosternal, accompanied by dyspnea, cough, and hemoptysis developing in a patient who has been immobilized or bedridden is suggestive of pulmonary embolism
- Pulmonary hypertensive pain may resemble angina in that it is precipitated by effort. Associated moderate or severe dyspnea and evidence of signs of pulmonary hypertension suggest its diagnosis
- Chest discomfort due to pericarditis is typically retrosternal, aggravated by coughing, deep respiration, or change in position; worse in supine, and relieved in sitting upright and leaning forward
- The acute onset of pleuritic pain and dyspnea in a patient with a history of asthma or emphysema is suggestive of pneumothorax
- Psychogenic chest pain is often associated with hyperventilation and other somatic symptoms such as chronic headache, dizziness, sweating, paresthesia, and a sense of 'impending doom'.

## RED FLAGS

- Lack of chest pain does not exclude IHD
- Over-reliance on tests with poor sensitivity, such as ECG, or on the initial values of cardiac biomarkers will miss many patients with MI
- In a patient with chest pain, the clinical response to *GI cocktail* (a mixture of liquid antacid, viscous lidocaine, and an anticholinergic), or sublingual nitroglycerin (NTG), cannot reliably identify the source of pain. Failure to respond to NTG should not be used to exclude the possibility of CAD<sup>7,17</sup>
- A history of a psychiatric diagnosis or overwhelming anxiety in a patient with



acute chest pain does not preclude the possibility of an acute coronary event.

## SELECTIVE GLOSSARY

**Cardiac syndrome X (CSX)<sup>§</sup>**— It is a condition defined by the presence of angina-like chest pain with angiographically normal coronary arteries which is observed in approximately 20–30% of angina patients undergoing coronary arteriography. To establish the diagnosis, patients must have evidence of stress-induced myocardial ischemia by exercise ECG, stress scintigraphy, or stress echocardiography, in conjunction with anginal chest discomfort. Coronary angiography reveals normal or near normal epicardial coronary arteries. Patients with CSX are usually younger (mean age 49 years) than patients with atherosclerotic CAD; more common in women (most of whom are perimenopausal) than men. Pain, which usually occurs at rest, may have atypical features. The exact pathophysiologic factors and mechanisms of pain in these patients are unclear. However, patients with chest pain and normal coronary arteries have abnormal vasodilatory coronary blood flow responses and an increased sensitivity of the coronary microcirculation to vasoconstrictor stimuli (microvascular angina). Microvascular endothelial dysfunction appears to be responsible for these coronary microcirculation abnormalities. Risk factors such as hypertension, hypercholesterolemia, increased plasma homocysteine levels, diabetes mellitus, abnormal blood rheology, *H. pylori* infection, and smoking can contribute to its development. Most patients with CSX are postmenopausal women and estrogen deficiency has been

therefore proposed as a pathogenic factor in female patients. Recently, techniques such as functional angiography, SPECT, and stress MRI have been used to diagnose CSX. However, the diagnosis remains one of exclusion. CSX has a low mortality rate and an excellent prognosis despite variable symptomatic improvement.

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<sup>§</sup>CSX must be distinguished from metabolic syndrome x of insulin resistance (glucose intolerance), hypertension, hyperlipidemia, elevated BMI, and frequently associated with abnormal coronary angiography.



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## CHAPTER

# 9

## Constipation

### SYNOPSIS

The definition of *constipation* varies substantially among patients, physicians, and researchers; and includes expressions such as infrequent bowel movements (too infrequent), incomplete evacuation with small feces (too little), difficult bowel movement, inability to evacuate at will, straining at stooling, or a need for digital manipulation to enable defecation (too hard).<sup>1,2</sup>

The frequency, consistency, and quantity of stools also vary depending on an individual's diet, fluid intake, physical activity, lifestyle, and social factors.<sup>3</sup> In many patients the complaint of constipation reflects a mistaken perception of what constitutes normal bowel habits\*.<sup>4</sup> Because of the subjective nature of the condition, no consensus exists on the definition of constipation.

However, a working definition of constipation may be described as decreased stool frequency from the patient's usual pattern, with or without difficult passage of small, hard stools, *provided* it does not represent a recent change in

bowel frequency, and is not associated with symptoms such as pain on defecation or distension.

In clinical practice, constipation is generally defined as fewer than three bowel movements per week. An alternative (Rome III) definition for *functional chronic constipation* in adults is two or more of the following criteria<sup>†</sup> for at least 12 weeks, not necessarily consecutive, in the preceding 12 months (without use of laxative):

- Fewer than three bowel movements per week
- Excessive straining during at least 25% of bowel movements
- Sensation of incomplete evacuation after at least 25% of bowel movements
- Passage of hard or pallet-like stools in at least 25% of bowel movements
- Manual maneuvers (e.g. digital evacuation) to facilitate more than 25% of bowel movements.

The information acquired from the history and examination largely determines the investigations required.<sup>5</sup> Majority of chronic constipation patients can be managed depending on

\* A common saying is, "One man's constipation is another man's diarrhea."

<sup>†</sup>These criteria should not be applied to diagnose constipation caused by underlying organic disease.

clinical assessment; however, the recently published evidence-based recommendations by the American College of Gastroenterology Task Force on Chronic Constipation serve as a useful guide in patients with sinister features at the outset.<sup>6</sup>

## DIFFERENTIAL DIAGNOSIS

### Common

- Lifestyle
  - Low calorie diet
  - Low fiber diet
  - Deficient fluid intake
  - Immobility
  - Repressed defecatory urge
- Laxative/enema abuse
- Painful anal lesion (Fissure, hemorrhoids, abscess, rectal prolapse)
- Irritable bowel syndrome with constipation (i.e. IBS-C)
- Psychological (depression, anxiety)
- Medication (Opioids, antacids, iron supplements, calcium channel blockers, anticholinergics, antiparkinsonian drugs, antidepressants, antipsychotics).

### Occasional

- Eating disorder (anorexia nervosa, bulimia)
- Intestinal obstruction (volvulus, strangulated hernia, intussusception, or extrinsic compression by any growth)
- Inflammatory bowel disease (IBD)
- Endocrine disease (Hypothyroidism, diabetes mellitus)
- Neurologic disease (stroke syndromes, dementia, spinal cord disease—paraplegia, cauda equina lesion, tumors)
- Metabolic disorder (hypokalemia, hypercalcemia, uremia)
- Postsurgical (abdominal, pelvic, colonic, anorectal).

### Rare

- Diverticulosis
- Carcinoma of the colon
- Neurologic (Parkinson's disease, multiple sclerosis)
- Pelvic floor dysfunction (PFD : *vide infra* ↓↓)
- Developmental abnormality (Hirschsprung's disease : *vide infra* ↓↓).

## INVESTIGATIONS—GENERAL

### CBC

- Low Hb level due to occult blood loss in colonic malignancy.

### ESR

- Elevated in inflammatory or malignant bowel lesion.

### FOBT

- In chronically constipated middle-aged or elderly adults, and in at-risk individuals (family history of colonic cancer, change in stooling pattern, weight loss, blood in stools, abdominal mass), FOBT may be useful to assess an obstructing neoplasm of the colon. Perianal lesions can give false-positive results.

### Proctoscopy (Anoscopy)

- For presence of internal hemorrhoids, fissure, ulcer, growth, polyp, or stricture; biopsy (Bx) can be obtained to confirm the diagnosis.

### Urea, Creatinine, Electrolytes

- Elevated urea, hypokalemia with dehydration and intestinal obstruction.

## INVESTIGATIONS—SPECIFIC

### Endocrine Panel

- High TSH with low T4 in myxoedema.

- High blood glucose in uncontrolled chronic diabetes mellitus complicating autonomic neuropathy.

### Serum Calcium

- Elevated in malignancy, and hyperparathyroidism.

### AXR

- Dilated bowel loops with multiple fluid levels in intestinal obstruction.
- May provide evidence for an excessive amount of stool in the colon.

### US Abdomen

- To assess extrinsic abdominal or pelvic compression (e.g. pregnancy, fibroid, tumor).

### Colonoscopy

- Preferred procedure in patients at risk (i.e. with warning signs) for colon cancer or IBD.
- Enables biopsy (Bx) of suspicious lesion, and remove any high impaction.

### Sigmoidoscopy/Barium Enema

- May be appropriate in younger patients who are not at risk for colon cancer. Polyps, diverticula, strictures, and luminal wall lesions can be demonstrated.

### MRI—Brain, Spine

- As indicated in multiple sclerosis, spinal trauma, spinal disease.

### Expanded Physiological Studies (Table 9.1)<sup>1</sup>

- In patients with chronic constipation with no identifiable cause following initial evaluation, and in whom initial treatment has failed, or in those patients wherein subtypes of constipation are suspected, such as colonic motility dysfunction, or pelvic floor dysfunction, following studies may be helpful.<sup>7</sup>

**Table 9.1:** Anorectal and pelvic floor function tests<sup>1</sup>

<ul style="list-style-type: none"> <li>• Ultrasonography</li> <li>• Anorectal manometry</li> <li>• Defecation proctography</li> <li>• Balloon expulsion test</li> <li>• Rectal sensation – mechanical and electrical</li> <li>• Pudendal nerve terminal motor latencies</li> <li>• Perineometry</li> <li>• Measurement of rectoanal angle</li> <li>• Sphincter/puborectalis electromyogram</li> <li>• Spinal evoked potentials by rectal stimulation</li> <li>• Cerebral evoked potentials by rectal stimulation</li> <li>• Scintigraphic expulsion of artificial stool</li> </ul>
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- Anorectal manometry—Mainly to exclude adult-onset or short segment Hirschsprung disease.
- Barium defecography—To evaluate evacuatory disorders such as rectal prolapse, enterocele, and rectocele.
- Colonic transit studies (using radiopaque marker)—To study colonic motility disorders. In normal persons, most of the markers should pass by day 5; in a patient with slow colonic transit, the markers will be scattered throughout the colon. If the patient has pelvic outlet obstruction, more than 20% of the markers will be held up in the rectum.
- Balloon expulsion studies—To demonstrate impaired rectal evacuation.

### Rectal Biopsy

- Helpful to diagnose Hirschsprung's disease, ulcerative colitis, Crohn's disease, and infiltrative diseases such as scleroderma, and amyloidosis.

## CLINICAL NOTES

- The initial step is to define the nature of the patient's bowel habit, and how the current problem differs from the normal pattern. History should include:
  - Detailed inquiry into the patient's normal pattern of defecation

- Amount of time spent on the toilet while waiting to defecate
- Whether the patient is c/o decreased frequency of stools, or painful/incomplete evacuation
- Perceived hardness of the stools
- Whether the patient strains in order to defecate
- What maneuvers (pharmacological or physical) are used to facilitate this process
- Any other symptoms (pain, protruding mass, bleeding) the patient may be experiencing
- Is the constipation acute or chronic—Constipation is generally considered to be acute or occasional if it's less than three months, and chronic if it lasts three months or more
- In acute constipation there is abdominal pain and vomiting, suggesting the possibility of intestinal obstruction. The most common cause of acute constipation in the elderly is fecal impaction. The diagnosis is made by DRE by the presence of firm, clay-like mass indicating impaction
- The most common cause of chronic habitual constipation is usually a combination of poor diet low in fiber (fast foods/eat on the run), decreased fluid intake, physical inactivity, and failure to acknowledge "call to toilets"<sup>‡</sup>
- Diet—Inquiry about a typical day's diet should include the type and quantities of fiber, fluid, fruits, vegetables, as well as any recent change in diet
- Medications—Reviewing medications and discontinuing any responsible drug will relieve constipation
- Risk factors—In adults inquiry about risk factors for colon cancer such as unintentional

weight loss, change in bowel habits (Table 9.2), nausea, vomiting, abdominal pain, distension, presence of blood in the stools, family history of colon cancer is important.

**Table 9.2:** Differential diagnosis of change in bowel habit (constipation/diarrhea)

**Constipation dominant**

- Low-fiber diet
- Drug effect — For example codeine, iron, laxative abuse
- IBS
- Diabetic neuropathy (autonomic neuropathy)
- Fecal impaction
- Carcinoma of colon, rectum, or anus
- Neurologic disease such as spinal cord injury

**Diarrhea dominant**

- Viral gastroenteritis
- Food poisoning
- Parasite infection (giardiasis)
- Traveler's diarrhea (usually *Escherichia coli* infection)
- Change in resident bacterial flora, e.g. antibiotic associated diarrhea
- Antibiotic-related diarrhea (*Clostridium difficile* colitis)
- Hyperthyroidism
- Diabetic neuropathy (autonomic neuropathy)
- Drug effect
- Lactose intolerance
- Gluten sensitivity (celiac sprue)
- Crohn's disease
- Diverticulitis (infection of a diverticulum)
- Food intolerance
- IBS
- Ulcerative colitis
- Whipple's disease
- Malabsorption syndrome

- Depression—Constipation can be a significant symptom in all types of depressive illness and may be aggravated by treatment with depression
- IBS—With IBS the patient may c/o constipation or diarrhea or both alternating. Associated somatic and psychological complaints such as anxiety, depression, chest pain, headache, fatigue, myalgias, and gynecologic symptoms strongly favor the diagnosis of IBS
- Systemic disease—Diabetic neuropathy may result in constipation due to chronic dysmotility, and slow transit time. Symptoms

<sup>‡</sup>'Dyschezia' or lazy bowel is the term used to describe a rectum that has become unresponsive to fecal content and this usually follows repeated ignoring of calls to defecate.

such as cold intolerance, hair and skin changes suggest myxoedema. Any cause of hypercalcemia, e.g. hyperparathyroidism, and malignancy may cause constipation. The patient may also c/o abdominal pain, vomiting, nocturia, and mental symptoms associated with this condition. A neurological examination may detect signs of CVA, dementia, Parkinson's disease, spinal cord disease, or multiple sclerosis

- Past history—A long history of bowel obsession<sup>§</sup>, abdominal surgery, radiation therapy, may suggest the cause of constipation.
- Physical examination—For weight, nutritional status, thyroid, and abdomen (tenderness, mass, distended bowel loops)
- PR—It is an important procedure because about one-fourth of cancers are within reach of the examining finger. Lesions such as hemorrhoids, fissure, ulcer, impaction, growth, fecal occult blood are obvious
- Anal wink—Sensation of the perianal area and the 'anal wink' (a reflex constriction upon pinprick sensation of the perianal area; mediated by S2, S3, S4) reflex should be tested in spinal cord disease or lumbosacral roots
- Constipation from infancy may be due to Hirschsprung's disease. Occasionally symptoms may present for the first time in adult life
- Lifelong constipation (severe refractory constipation) is sometimes due to megacolon.

## RED FLAGS

- Alarm symptoms and signs in patients with constipation include:
  - Persistent anemia
  - Positive FOBT
  - Hematochezia

<sup>§</sup>The older generation considers defecation every day a sign of good health.

- Significant weight loss
- Therapy resistant constipation
- New onset constipation in elderly without obvious cause
- Family history of IBD
- Family history of colon cancer.
- Intermittent colicky abdominal pain with distension and progressive constipation or obstipation is an urgent indication to evaluate the cause of intestinal obstruction
- Sexual abuse is a known cause of chronic constipation and needs to be excluded in patients especially with psychosexual problems.

## SELECTIVE GLOSSARY

**Hirschsprung's disease** (Congenital Megacolon)—Abnormally large or dilated colon due to congenital absence of myenteric ganglion cells in a distal segment of the large bowel, and resultant loss of motor function in this segment causes massive hypertrophic dilatation of the normal proximal colon, appears soon after birth, is called "Hirschsprung's disease". Signs and symptoms (abdominal distension, vomiting, constipation, etc.), may vary with the severity of the condition. Sometimes they appear after birth; other times they may not be apparent until the child becomes a teenager or adult.

**Pelvic floor dysfunction (PFD)**—The pelvic floor muscles support the pelvic organs, bladder and rectum, and their function is critical to activities such as urinating, having bowel movements, and sexual intercourse. PFD has traditionally been described as resulting from laxity or poor tone of the pelvic floor musculature and/or ligaments. Damage of this nature usually results from aging, straining, or trauma, resulting in complaints such as poor urine stream, constipation, low back pain, pain with ejaculation or



vaginal penetration, pelvic pain or pressure, or urinary frequency and urgency.

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## CHAPTER

# 10

## Convulsions

### SYNOPSIS

A *convulsion* is a violent spasm, or a series of involuntary contractions of the voluntary muscles, especially those affecting the face, trunk, or extremities. During convulsions, the person may cry out, fall to the floor unconscious, his or her body shaking rapidly and uncontrollably, drool, or even loose bladder control. Within minutes the attack is over, and the person regains consciousness, but is dazed, confused, and incoherent, or may be exhausted and asleep. This is the image most people have when they describe the symptoms of convulsions to physicians which is typical of tonic-clonic grand mal seizure (Table 10.1).

**Table 10.1:** Convulsions: common symptoms and signs

- Fits
- Body twitching
- Body spasm
- Head spasm
- Facial spasm
- Limbs jerking
- Loss of consciousness
- Limb paralysis
- Bladder incontinence
- Bowel incontinence
- Tongue bite
- Abnormal behavior
- Sleeping after fits

The term ‘convulsion’\* is often used interchangeably with *seizure*,<sup>†</sup> although there are many types of seizures. *Seizures* are attacks of cerebral origin consisting of sudden and transitory abnormal phenomena of a motor (convulsive jerking), sensory (light flashes, buzzing), autonomic (sweating, enuresis), automatic (abnormal behavior, memory lapse), or psychic nature (hallucinations), resulting from transient abnormal neuronal discharge of the brain, with or without loss of consciousness. Thus, paroxysmal changes in consciousness, sensation, emotion, or thought processes may all be the manifestations of a seizure disorder *without* its motor component of convulsions, which are termed as *nonepileptic seizures* (i.e. NES: Table 10.2), especially those subclassified as psychogenic origin, i.e. *psychogenic nonepileptic seizure* (PNES).<sup>1</sup>

\*The special problems posed by children with convulsions are not addressed.

<sup>†</sup>‘Seizure’ is a sudden act, action, or attack of seizing something (as of disease), especially the physical manifestations as convulsions; and the clinician should certainly refrain from diagnosing a first seizure as epilepsy.

**Table 10.2: Nonepileptic seizures (NES): Differentiation**

Two major types of NES are recognized; their differentiating features being as follows:

- *Psychogenic* NESs are symptoms of an underlying psychiatric disorder, without a physiologic basis, e.g. conversion disorder, anxiety disorder, PTSD, psychotic disorder, factitious disorder.
- *Physiologic* NESs are caused by physiologic dysfunction, such as cardiac arrhythmias, hypotensive episodes, cerebrovascular disease, complicated migraine, parasomnias, tics, and spasms. Such conditions may result in loss of consciousness, with or without associated motor manifestations. A detailed history and appropriate investigations (e.g. Holter monitoring, noninvasive carotid artery studies, or tilt-table testing) will usually reveal the true diagnosis.

**Note:** Most of the discussion in this article pertains to *psychogenic* NESs, i.e. PNES.

*Epilepsy*<sup>†</sup> is a symptom complex in which there is a tendency to have repeated (two or more), *unprovoked* seizures, requiring definitive diagnosis and treatment. Not everyone who has seizures has epilepsy, but everyone who has epilepsy has seizures.

Neither convulsions, seizures, nor epilepsy are a final diagnosis, but are symptom complexes requiring a search for underlying etiologic factors. Further, it is extremely important to differentiate epileptic seizures, including various simple partial seizures, complex partial seizures, typical and atypical absence seizures from NES, because misdiagnosis leads to inappropriate treatment with antiepileptic drugs, leading to toxic side effects, causing additional disability and frustration.

## DIFFERENTIAL DIAGNOSIS

### Common

- Syncope (vasovagal, orthostatic hypotension, cardiac arrhythmia)

<sup>†</sup>The word 'epilepsy' is derived from the Greek word for 'attack', (presently meaning seizure). People once thought that those with epilepsy were being 'attacked' by demons or Gods. However, in 400 BC Hippocrates suggested that epilepsy was a disorder of brain.

- CNS infection (bacterial, TB, viral-HIV, cerebral malaria, cysticercosis)
- Seizures (generalized tonic-clonic, partial-simple, status epilepticus)
- Cerebrovascular accident (TIA, stroke)
- Head injury (early or late)
- Hypoglycemia
- Malignant hypertension (hypertensive encephalopathy)
- Toxemia of pregnancy.

### Occasional

- Migraine (complicated)
- Alcoholism/withdrawal (rum fits)
- Metabolic (electrolyte imbalance, hypocalcemic, DKA, uremia, hepatic encephalopathy, cardiac arrest)
- Drug toxicity (aminophylline, theophylline, ephedrine, terbutaline, bupropion, penicillin, insulin, metronidazole, pentazocine, lidocaine)
- Substance abuse (amphetamines, 'ecstasy', antidepressants, antipsychotics, cocaine).

### Rare

- Pseudoseizure<sup>§</sup> (i.e. PNES)
- Infections (tetanus, rabies)
- Brain tumors (primary/secondary)
- Degenerative disorders (dementia, multiple sclerosis)
- Sleep disorders (parasomnias)
- Poisoning (organophosphate insecticides, cyanide, strychnine).

## INVESTIGATIONS—GENERAL

### CBC

- Leukocytosis may suggest CNS infections.
- Erythrocytes may show sickled cells.
- Polycythemia with elevated hematocrit in hypercoagulable states.

<sup>§</sup> The term *nonepileptic seizure* is preferred to *pseudoseizure*, because the former term is nonjudgemental, and describes problem without implying causation.

### Blood Glucose

- In diabetics and DKA.

### Serum Electrolytes

- Hyponatremia, hypokalemia, hypomagnesemia, hypoglycemia, and hypocalcemia can precipitate seizures.

### ECG

- To identify cardiac rhythm, detect possible cardiac ischemia, and measure QT-interval. Prolonged QT syndrome often presents with simple or convulsive syncope.

### Neuroimaging

- CT head is indicated in an emergency, e.g. when seizures are due to head trauma, decreased level of consciousness, or a new neurologic deficit is evident. Otherwise, waiting for a more definitive imaging with MRI (for mass lesion, vascular malformation, stroke, cysticercosis, and multiple sclerosis) should be considered.

### Biochemistry Panel

- LFTs, urea, creatinine, and VDRL as indicated.

## INVESTIGATIONS—SPECIFIC

### CSF

- CSF evaluation in febrile and immunocompromised patients suspected with bacterial, viral, and fungal infection.
- In patients with systemic malignancy, CSF cytology can identify meningeal carcinoma.

### EEG

- Can help to establish the presence and type of seizure. Both interictal (between seizures) and ictal findings (during a seizure) are used in evaluating seizure and epilepsy disorders.
- A normal EEG, however, does not exclude the possibility of epilepsy or seizures. Often

abnormalities are seen after several EEGs have been obtained. The yield of the test is enhanced by using sleep deprivation activating procedures (e.g. hyperventilation, photic stimulation), increasing the recording time, and capturing sleep during testing.

### Ambulatory EEG (aEEG)

- In selected cases with recurrent events, and nondiagnostic EEG findings, or lack of response to treatment.
- Also useful in separating true seizure from pseudoseizure, or other paroxysmal abnormal behavior, especially when the two coexist.

### Video-EEG Monitoring<sup>2,3</sup>

- May be essential in difficult cases to distinguish between epileptic and NES. Video-EEG recordings of the actual event provide a correlation of clinical and EEG findings, and a means to assess their evolution and resolution.

### Toxicology (Serum and Urine) Screen

- For drugs and alcohol, especially if an adequate history cannot be obtained.

## CLINICAL NOTES

- Although in the majority of the patients with convulsions attending their physicians are known to be suffering from some kind of seizure disorder, in others the physician usually does not witness the seizures, and must rely on information provided by the patient, an outside observer, or both. However, every patient must be assessed in detail, for if they are not, the systemic disorder that may have triggered the attack will be missed
- Listen to the patient—Not all jerks, shakes, tics, tremors, spasms, and dystonia are convulsions. Therefore, the initial task, when a patient presents with convulsions, is to determine whether the attack in question had indeed features of *true* seizure

- Listen to the eyewitness—An accurate record from an observer is invaluable, particularly if there is evidence that his/her attack was the first one. This record should include:
  - Details of the circumstances of the attack (anxiety, panic, pain, prolonged standing, physiological acts, e.g. micturition).
  - Any prodromal symptoms (aura, e.g. odd behavior, repetitive actions).
  - Details of the sequence of events of the attack itself (e.g. a rhythmic flexion-extension movement of the extremities, loss of consciousness, incontinence, tongue biting).
  - The aftermath - whether the episode was followed by period of (postictal) con-fusion.
- These observations, especially presence or absence of aura, and postictal confusion are critical and help to differentiate seizures from syncopal and other common *physiologic* NES, such as postural hypotension, TIA, complicated migraine, sleep disorders, and *psychogenic* NES (Table 10.3)
- What is the cause of seizure? Knowledge of patient's medical history, including family history, aids in the understanding the cause of convulsion or seizure. A history of head trauma, fever, infection, alcoholism, and systemic disease such as diabetes mellitus, hypertension, cerebrovascular disease, and metabolic disturbances suggest the cause of seizure
- Medications and substance abuse—A review of patient's medications is important. Bronchodilators (aminophylline, theophylline, terbutaline, ephedrine); antidepressants (bupropion, amitriptyline, imipramine); antipsychotics (thioridazine, clozapine, haloperidol); opioids (tramadol); anesthetics (lidocaine, pentazocine, fentanyl); antimicrobials (penicillin, metronidazole, isoniazid); antineoplastics (vincristine, methotrexate), 'ecstasy', etc. are known to provoke seizure.
- *Pseudoseizure*, i.e. *PNES* (Table 10.4)—The

**Table 10.3:** Differentiation between syncope and seizure

Parameter	Syncope	Seizure
Onset	Gradual	Sudden
Attack	Rapid, but never absolutely sudden; may be averted by lying down promptly	Loss of consciousness with absolute suddenness; cannot be averted
Position at onset	Usually erect or on change to erect; rarely recumbent	Any
Warning symptoms	Light headedness, dizzy, giddy, nausea, vomiting	Unusual sensations, sounds, smells, blurred vision, hallucinations, tingling, twitching of muscles
Convulsions	Rare	Common
Accompaniments	Incoherence, incontinence, tongue bruising rare	Confusion, enuresis, tongue bruising common
Duration	Variable—seconds to few minutes	About a minute
Sequela	No sequela after recovery from attack	Confusion, headache, drowsiness, often deep sleep; postictal paralysis may be present
EEG	Normal	Normal or abnormal

possibility of pseudoseizure should be carefully considered as prompt recognition can prevent subsequent intervention.

- Physical examination—A focused examination should be done soon after a paroxysmal event and should include:
  - Evidence for injuries, including head injury.
  - Check oxygen saturation.
  - Chest auscultation for possible aspiration.
  - Heart rate, rhythm, BP, ECG (hypertensive encephalopathy), and orthostatic changes (syncope, arrhythmias).

**Table 10.4:** Difference between seizure and PNES (Pseudoseizure)

Parameter	Seizure (tonic-clonic/grand mal)	PNES (Pseudoseizure)
Setting	Anywhere, anytime, also during sleep	Often in public, never during sleep
Attack	Tonic-clonic spasms	Bizarre nature
Accompaniments	Mostly stridor due to laryngeal spasm	Mostly moans and groans, vocalization
Sequelae	Patient may fall, may be injured, or tongue bruising, incontinence of urine and faces	Patient never falls, no injury, no tongue bruising, not incontinent
Consciousness	Brief period of loss of consciousness common	Consciousness is retained (but loss of consciousness may be stimulated)
Plantars	Extensor, bilaterally	Remain flexor
Pupils	Dilated	Unchanged
Eyelids	Opens easily, passively	Patient screws up eyelids when an attempt is made to open them
Blood pressure, heart rate	Increased	Do not alter
Serum prolactin levels	Often increased	Often normal
CPK	Increases	Often normal
EEG	Normal or abnormal	Normal

- Carotid auscultation for bruits / murmur (sources of embolic stroke).
- Presence of postictal phenomenon, i.e. Todd's paralysis.
- Fundoscopy—For evidence of papilledema, indicating ICP caused by an intracerebral hemorrhage, or space occupying lesion.
- Neurologic deficit—Dysarthria, facial asymmetry, or right or left hemiparesis. Pupillary asymmetry may indicate brainstem herniation.
- If the patient is drowsy, the *Glasgow Coma Scale* should be used to provide an objective measure to any subsequent change in the level of consciousness.
- Psychologic testing—Psychologic testing may help distinguish patients with NES from those with epileptic seizures. The Minnesota Multiphasic Personality Inventory<sup>4</sup> and other inventories, such as the Washington Psychosocial Seizure Inventory can have a role in this regard.<sup>5</sup>

## RED FLAGS

- New onset of seizures in the elderly may indicate serious disorder such as CVA, tumor, including alcoholism, and drug abuse; detail investigations are indicated<sup>6, 7</sup>
- In obscure cases, consider unusual presentation of systemic disorder, e.g. sarcoidosis, porphyria<sup>8</sup>
- Discovery of papilledema should lead to urgent investigations and treatment
- Consider inadvertent or unrecognized drug or alcohol withdrawal or illicit drug use. Obtain urine toxicology. An amphetamine derivative, *Ecstasy*, (Methylenedioxy-methamphetamine—MDMA) often cannot be detected by standard toxicology screens; these substances can present a vexing problem for clinicians faced with symptoms from a totally unknown cause.<sup>9</sup>

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## CHAPTER

# 11

## Cough

### SYNOPSIS

*Cough* may be defined as a sudden and variable expiratory thrust of air from the lungs and through the air passages, associated with phonation, which momentarily interrupts the physiological pattern of breathing.

The act of cough is an important physiologic pulmonary defence mechanism which is beneficial in most instances; it helps to keep the lower respiratory passage clear, protects against entry of foreign materials from outside, and prevents stagnation of secretions within the air passages. Nevertheless, in many patients cough may be troublesome, sometimes distressing, due to associated symptoms such as exhaustion, insomnia, fever, hoarseness, body aches and pains, or its complications such as rib fracture, urinary incontinence and syncope, which can lead to decrease in a patient's health-related quality of life.

Clinically, cough is generally divided into two groups: productive cough that is accompanied by sputum, and nonproductive cough, which is dry and does not produce any sputum. Based on its duration, cough is said to be acute—less than some arbitrary duration of 3 weeks, and

chronic/persistent—when more than 3 weeks. Acute cough, in the great majority of healthy adults, is minor and self-limiting, although the possibility of serious cause such as acute pulmonary edema, asthma exacerbation, pulmonary embolus, and pneumonia should always be kept in mind. It is the chronic/persistent variety that usually prompts patients to seek medical care. In many patients, chronic cough is either pathologic by itself, e.g. bronchial asthma, TB, malignancy, or a manifestation of systemic disease, e.g. mitral stenosis, GERD, and LVF that requires attention. In some instances, chronic cough may manifest as an acute event, such as an acute exacerbation of chronic bronchitis. In recent times, whooping cough (pertussis), a preventable infectious disease in pediatric age group, is being documented frequently in adults too as the cause of chronic cough (Table 11.1).<sup>1,2</sup> However, it is observed that, in patients with uncontrolled and unexplained persistent cough, with expensive work-up and medications, and frequent visits to the physician, as well as the patient's and family's distress and concern about an underlying disease, may cause significant psychological stress, including

anxiety, frustration, anger, and irritability. Therefore, it is suggested that, in the diagnosis and management of chronic cough, along with clinical efficacy and cost-effective considerations, psychological issues related to patients' satisfaction should also be taken into account in formulating guidelines.<sup>3-5</sup>

**Table 11.1:** The return of whooping cough: why?

- Failure of children to receive full immunization schedule as recommended; i.e. five shots by age 7.
- Failure of full protection in spite of completing recommended immunization schedule.
- Protection from vaccines given in early childhood diminishes over time, offering little or no protection five to 10 years after the final injection, so that pertussis can occur in such subset of older vaccinated individuals, who may then infect susceptible infants and individuals.
- Atypical presentation of pertussis in adolescents and adults; symptoms may be indistinguishable from those of other upper respiratory infections.
- Physicians often do not include whooping cough in the differential diagnosis of a persistent cough.
- Failure to comply with treatment regimen during pertussis outbreaks.

## DIFFERENTIAL DIAGNOSIS

### Common

- Irritants (cigarette smoke, pollutants, allergens)
- URTIs
- Postinfectious cough<sup>6</sup> (generally after URTI)
- Sinusitis
- Upper airway cough syndrome (UACS)<sup>\* 7</sup>
- Allergic rhinitis
- Asthma exacerbation
- Acute bronchitis
- Pneumonia
- Tuberculosis
- GERD

\* Formerly called Postnasal drip (PND).

- LVF
- Drugs (ACE inhibitors, beta blockers, aspirin).

### Occasional

- COPD
- Bronchiectasis
- Pleural effusion
- Lung abscess
- Cardiac (mitral stenosis)
- Immunodeficiency (Pneumocystis carinii pneumonia, i.e. PCP)
- Whooping cough.

### Rare

- Inhaled foreign body
- Interstitial lung disease
- Bronchogenic carcinoma/secondaries
- Lymphoma
- Aspiration
- Eosinophilic pneumonia (Löffler's syndrome, Tropical eosinophilia, parasitic, fungal)
- Medications – (nitrofurantoin, sulfonamide, hydralazine, methotrexate, cyclophosphamide)
- Ear wax, hair, foreign body in ear canal (Arnold's reflex)
- Psychogenic cough, habit cough, tic cough.

## INVESTIGATIONS—GENERAL

### CBC

- WBC count raised in bacterial infection
- Anemia characteristic of chronic disease common
- Eosinophilia in allergic conditions
- Marked lymphocytosis in pertussis.

### Sputum

- Gram stain, acid fast stain and culture for specific organisms

- Sputum eosinophilia in asthma and non-asthmatic eosinophilic bronchitis (NAEB)<sup>†</sup>

### CXR

- Helpful in evaluating for:
  - Pneumonia (consolidation)
  - Bronchiectasis (dilated tubular or cystic mucus filled bronchi)
  - COPD (hyperinflation, flat diaphragm)
  - TB (upper lobe infiltrates, hilar lymphadenopathy, cavitary lesions, pleural effusion)
  - Sarcoid (hilar lymphadenopathy)
  - CHF (pulmonary edema, vascular congestion, Kerley B lines, peripheral infiltrates, pleural effusion, cardiomegaly)
  - Bronchogenic carcinoma (hilar mass or a single coin shadow).
- A normal CXR in an immunocompetent patient with chronic cough usually excludes tuberculosis, bronchiectasis, persistent pneumonia, bronchogenic carcinoma, and sarcoidosis. However, chronic cough can be a cause of many disorders in spite of a normal CXR; a few of such conditions are given in Table 11.2.

### Peak Expiratory Flow Rate (PEFR)

- Serial measurements of peak flow rates on waking, i.e. early morning, during day, and before bed, demonstrating wide variations in airflow limitation is seen in asthma, and facilitates monitoring its treatment.

## INVESTIGATIONS—SPECIFIC

### PFTs

- Can differentiate obstructive, e.g. asthma, COPD, from restrictive disease, e.g. sarcoidosis, pneumoconiosis.

<sup>†</sup>NAEB—a recently defined clinical entity with high eosinophilic count in induced sputum, that manifests similarly to, but is distinct from asthma in that there is neither reversible airway obstruction nor airway hypersensitivity as defined by a positive methacholine challenge.

**Table 11.2:** Causes of chronic cough among adults with normal CXR

Diagnosis	Differential diagnosis with normal CXR
Environmental	Tobacco exposure; industrial pollutants; occupational allergens
Infections—respiratory	Postinfectious cough; chronic bronchitis; TB; bronchiectasis; tropical pulmonary eosinophilia; whooping cough
Infections/disorders—ENT polyp;	Cerumen; Otitis media with effusion; chronic sinusitis; nasal vocal cord dysfunction/paralysis; aspiration
Asthma	Cough-variant asthma; postinfectious hyperactivity airways
Cardiac	CHF; mitral stenosis
GI disorders	Gastroesophageal reflux
Neoplasia	Bronchial adenoma; mediastinal mass with tracheal compression; laryngeal papilloma, hemangioma
Iatrogenic	Drug induced; Foreign body – nose; ear; trachea; larynx; bronchus
Psychogenic	Habit cough; tic cough; psychogenic cough

### Pulse Oximetry

- To monitor arterial O<sub>2</sub> saturation in patients with asthma or COPD.

### pH Studies

- Ambulatory 24-hour esophageal pH monitoring is the most reliable but invasive test for GERD. It should, therefore, be performed only after failure of empiric GERD treatment, and a negative evaluation for asthma and sinusitis.

### CT Chest/MRI

- More sensitive for evaluating patients with equivocal or negative CXR findings.
- Assists in evaluating for mass lesions of neoplasms, sarcoid, ILDs, and bronchiectasis.

### CT Sinus

- For diagnosing chronic sinusitis, UACS.

**Esophagogastroduodenoscopy (EGD)**

- To evaluate GEDR or its complications such as esophagitis, ulceration, stricture, Barrett's esophagus, and adenocarcinoma.

**Bronchoscopy**

- Generally indicated in patients with:
  - CT/MRI suggesting neoplasm and their biopsy procedures
  - Foreign body aspiration
  - Chronic, persistent cough with negative clinical and lab work out
  - Cough with hemoptysis.

**Purified Protein Derivative (PPD) Skin Test**

- Performed in patients with high risk of pulmonary TB. Results are read within 48–72 hours of placement. Test is considered positive if skin erythema measures  $\geq 5$  mm for HIV-infected and other immunocompromised individuals;  $\geq 10$  mm for those at high risk; and  $\geq 15$  for all others.

**HIV Serology**

- In a HIV positive patient CD4+ lymphocyte count should be obtained; if it's below 200 / mm<sup>3</sup>, a more intensive evaluation for opportunistic infection, such as PCP, TB is indicated.

**Culture of Nasopharyngeal Secretions/PCR<sup>†</sup>**

- For the diagnosis of *B. pertussis* (Whooping cough).

**Sputum Cytology**

- May be helpful if history or CT/MRI suggest neoplasm.

**CLINICAL NOTES**

- Important historical features to be elicited are: normal (as a part of local irritation due to viral URTI) versus pathological cough; acute versus chronic cough that persists for 3 weeks or longer; and respiratory versus nonrespiratory causes
- Generally, in patients with chronic cough, neither the patient's description of his or her cough in terms of its character or timing, nor the presence or absence of sputum production, is helpful to rule in or rule out a diagnosis or to determine the clinical approach
- Does the patient smoke – its frequency and duration; are there any occupational and environmental exposures? Is there any clear triggering or relieving factor?
- Associated red flag symptoms, including hemoptysis, weight loss, night sweats and fever, and concomitant risk factors for malignancy, HIV, and drug abuse (cocaine lung) are very significant in the evaluation of chronic cough
- Some physical signs which may provide etiological clues are: sinus tenderness (sinusitis); conjunctival injection, rhinitis (URTIs); consolidation (pneumonia); fine crackles (pulmonary edema); localized wheeze (obstructive lesion – tumor, foreign body); cardiac – (murmur in valvular disease, S<sub>3</sub> in CHF); ear canal – wax, hair (Arnold's reflex)
- Ask specifically about UACS, i.e. postnasal drip, as patients often do not volunteer this information
- Although some evidence suggests that UACS is a common cause of chronic cough, it is an entity without a clear definition and no pathognomonic findings. It is usually diagnosed in the presence of suggestive symptoms such as rhinorrhea, nasal congestion, a sensation of drainage or tickle in the oropharynx, and throat clearing, with or without mucoid secretions visualized in

<sup>†</sup> PCR confirmation is not recommended as there is no universally accepted, validated technique for routine clinical testing.

the posterior pharynx. Its role in chronic cough, though controversial, is supported by response to therapy — usually an antihistamine-decongestant combination drug or nasal corticosteroid spray<sup>8</sup>

- Cough due to ACE inhibitors is a class effect and has been documented with all ACE inhibitors in use; changing to another agent will not ameliorate the symptoms
- A past history of recurrent lung infections from childhood is suggestive of cystic fibrosis and bronchiectasis; a history of hay fever and eczema suggests asthma; while tuberculosis, emphysema (alpha1-antitrypsin deficiency) asthma, cystic fibrosis have a familial predisposition
- In a healthy individual, cough, following URTI and persisting for at least 3 weeks, but no more than 8 weeks, consider the diagnosis of postinfectious cough. In some patients, transient bronchial hyperreactivity may be demonstrated
- In all patients with chronic cough, even in the absence of clinical signs or symptoms, consider UACS, asthma, and GERD, as they may present only as cough, and no other associated clinical findings, i.e. 'silent' UACS, cough-variant-asthma, and 'silent' GERD respectively
- In a nonsmoking patient with a clear chest radiograph who does not use ACE inhibitors, one or more of the following four causes of chronic cough account for the overwhelming majority of cases; namely, UACS, asthma, NAEB, or GERD.

## RED FLAGS

- A normal lung examination does not exclude asthma, bronchitis, COPD, GERD or lung malignancy
- Failure to improve with appropriate management over 4 weeks signals a need for detail work up to exclude TB, cough variant asthma, resistant pulmonary infections, malignancy, and immunosuppression

- In a patient with chronic bronchitis, any change in the character of the cough or sputum may be the presenting feature of a superimposed bronchogenic carcinoma
- *Smoker's cough* should not be neglected; it may be an early symptom of bronchogenic carcinoma. Conversely, bronchogenic carcinoma is known to occur in nonsmokers or in patients with other pulmonary conditions, such as chronic bronchitis
- When a patient has a cough lasting for >2 weeks without another apparent cause and it is accompanied by paroxysms of coughing, posttussive vomiting, and/or an inspiratory whooping sound, the diagnosis of a *B. pertussis* infection should be made unless another diagnosis is proven
- In patients with unexplained cough, evaluate the possibility of drug-induced cough.

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## CHAPTER

# 12

## Dementia

### SYNOPSIS

*Dementia* is an acquired neurological syndrome, common in the elderly, characterized by decline in memory and cognitive impairment, occurring in a state of clear consciousness (i.e. the patient is alert).

Although memory is the most common cognitive ability lost with dementia\*, other common findings include (Table 12.1):<sup>1</sup>

- Aphasia (i.e. difficulty with language, speech, comprehension, naming, reading, and writing);
- Apraxia (i.e. difficulty with motor actions, inability to perform previously learned tasks such as combing hair, dressing);
- Agnosia (i.e. difficulty with reorganization or comprehension of specific auditory, visual, and tactile stimulus); and
- Impaired executive functioning (i.e. impaired planning, organization, and judgement).

Symptoms may also include changes in:

- Personality (e.g. social inhibition, disinterest, explosive spells, mistrust of others, low moral character);

\* Three types of memory loss may exist in demented individuals, either individually or in combination; namely: *immediate memory*, i.e. difficulty in learning new information; *recent memory*, i.e. recalling recent events; and *remote memory*, i.e. remembering past personal information.

**Table 12.1:** DSM-IV-TR criteria for dementia

Development of multiple cognitive deficits manifested by both:

- Memory impairment (impaired ability to learn new information or to recall previously learned information)
- At least one of:

- Aphasia (language disturbance)
- Apraxia (impaired ability to perform motor activities despite intact motor function)
- Agnosia (failure to recognize or identify objects despite intact sensory function)
- Disturbance in executive functioning (e.g. planning, organizing, sequencing, abstracting)

Cognitive deficits significantly interfere with work or social activities and represent major decline from previous level of functioning.

Course characterized by gradual onset and continuing cognitive decline.

Cognitive deficits not due to any of the following:

- Other CNS conditions that cause progressive deficits in memory and cognition (e.g. cerebrovascular disease, Parkinson's disease, Huntington disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
- Systemic conditions known to cause dementia (e.g. hypothyroidism, vitamin B<sub>12</sub> and folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
- Deficits do not occur only during course of delirium
- Disturbance cannot be accounted for by any nonorganic mental disorder (e.g. major depressive disorder, schizophrenia)



- Mood (e.g. growing apathy, depression, withdrawal, anxiety, hallucinations); and
- Behavior (e.g. repetitive actions, or questioning; purposeless hyperactivity; wandering, agitation).

These clusters of symptoms and disabilities compromise the successful performance of activities of daily living in a demented individual (e.g. neglecting household chores, neglecting self-care, mistakes at routine work, difficulty handling money, trouble with shopping, and difficulty in driving).

Dementia does not occur *de novo*, but probably represents the end of a spectrum from normal aging through an intermediate state called *mild cognitive impairment* (MCI - *vide infra* ↓↓). Early identification of MCI is important because some of the disorders that cause dementia might be treatable, reversible, and preventable (Table 12.2). On the other hand, dementia tends to be progressive, cognitive functions tend to decline steadily, vegetative symptoms such as change in appetite, weight, sleep, and fatigue are often absent, and there is little or no response to medications. The typical differentiating features between MCI and dementia<sup>†</sup> are given in Table 12.3.

The task of a physician caring for a demented patient, therefore, is twofold:

- Early identification of those dementias that are treatable, especially because more treatment options are now available, and
- Educate and support the family of the patient with incurable dementia. Much can be achieved by careful analysis of the problems, defining what can be restored and what cannot, even if the condition is irreversible.

<sup>†</sup> There are a variety of 'dementias' which most frequently are categorized as *cortical* or *subcortical*. AD is the most well-known example of a cortical dementia. Subcortical dementias include Parkinson's, Huntington's, and AIDS dementia. The presentation of these two types of dementias differs.

**Table 12.2:** Potentially treatable/reversible dementias

- *Alcoholism:* Chronic
- *Connective tissue disorders:* Temporal arteritis, vasculitis, SLE
- *Drug toxicity*
- *Endocrine:* Thyroid disease, hyperglycemia, hypoglycemia, insulinoma, adrenal disease, pituitary disease, parathyroid disease
- *Infections:* Viral encephalitis, postencephalitis syndrome, chronic meningitis, AIDS, neurosyphilis
- *Mass lesion:* Chronic subdural hematoma (bilateral), tumor
- *Metabolic:* Dehydration, electrolyte disturbance, uremia, hepatic encephalopathy, hypercalcemia, hypoxia
- *Normal-pressure hydrocephalus*
- *Nutritional:* Vit. B<sub>12</sub>, folate, thiamine deficiency
- *Others:* Blindness, chronic seizures, CHF, dialysis encephalopathy, hearing loss, obstructive sleep apnea, radiation-induced
- *Psychiatric:* Depression

**NOTE:** Dementia due to alcoholism, HIV, TB, drugs, nutritional deficiency, and head trauma are preventable; the rest are amenable to therapy.

**Table 12.3:** Typical features differentiating mild cognitive impairment and dementia

#### *Mild cognitive impairment*

- Insidious onset – always
- Deficit involves memory
- Cognition remains intact
- No interference with social and occupational functioning
- May or may not eventually lead to dementia

#### *Dementia*

- Insidious onset – generally
- Impaired memory and one or more of the features of aphasia, apraxia, agnosia, and impaired executive functioning
- Cognitive deficits significantly interfere with work or social activities
- Deficit represents major decline from previous level of functioning
- Deficit cannot be explained exclusively by delirium, CNS disorders, or major psychiatric illness

## DIFFERENTIAL DIAGNOSIS

### Common

- Degenerative disorders (e.g. Alzheimer's disease, i.e. AD; Parkinson's disease, i.e. PD)
- Vascular dementia (i.e. VaD; e.g. multi-infarct dementia; single strategic infarct, lacunar state,

diffuse white matter disease, i.e. Binswanger's disease, hypoxic ischemic encephalopathy).

- Mixed dementia<sup>†</sup> (i.e. AD with VaD)<sup>2-4</sup>
- Infection (viral encephalitis, HIV-associated dementia complex/AIDS dementia complex, meningitis — TB)
- Substance abuse (alcoholism)
- Head trauma (chronic subdural hematoma, postconcussional syndrome)
- Intracranial causes (spaceoccupying lesions — tumors, abscesses).

### Occasional

- Drug toxicity/polypharmacy/interactions (e.g. anticonvulsants, anticholinergics, antihistamines, antiparkinsonian, narcotics, psychotropics)<sup>5, 6</sup>
- End-organ failure (cardiac/respiratory/hepatic/renal failure)
- Endocrine disorders (hypothyroidism)
- Neoplastic disease (primary cerebral tumors)
- Metabolic disorders (chronic electrolyte imbalance—hypocalcemia, hypercalcemia, hyponatremia, hypernatremia, hypokalemia, hepatic encephalopathy, uremia).

### Rare

- Degenerative disease (e.g. dementia with Lewy bodies<sup>§</sup>, i.e. DLB; Frontotemporal dementia\*\*, i.e. FTD; Pick's disease; Huntington disease).

<sup>†</sup>Mixed dementia is diagnosed when patients have evidence of AD and cerebrovascular disease, either clinically or based on neuroimaging evidence of ischemic lesions. Growing evidence indicates that vascular dementia and AD often coexist, especially in older patients with dementia.

<sup>§</sup>A Lewy body, described by Fredrick H Lewy, is an intracytoplasmic concentrically laminated round to elongated eosinophilic inclusion which often has a dense central core surrounded by a paler peripheral rim.

\*\*The term FTD covers both the temporal and frontal presentations of this condition: the frontal variant presents with insidious changes in personality and behavior, with neuropsychological evidence of disproportionate frontal dysfunction.

- Endocrinopathies (hyperinsulism, hyperparathyroidism, Addison's disease, Cushing's syndrome, hypopituitarism)
- Autoimmune disease (cranial arteritis, SLE, MS)
- Nutritional deficiency (e.g. thiamine, B<sub>1</sub>-Wernicke's encephalopathy; B<sub>12</sub>, folate-pernicious anemia; nicotinic acid-pellagra)
- Chronic infections (neurosyphilis)
- Prion disease (Creutzfeldt-Jakob disease, i.e. CJD)
- Normal pressure hydrocephalus (NPH - *vide infra* ↓↓)
- Hypoxic dementia (e.g. cardiac arrest, anesthetic accidents).

## INVESTIGATIONS—GENERAL

### CBC

- To exclude anemia, including macrocytic anemia with B<sub>12</sub> deficiency and infection.

### ESR

- May be elevated in infection, inflammation, neoplasm.

### Urea, Creatinine, LFTs

- Raised with renal failure.
- Increased bilirubin and transaminases with liver failure.

### Electrolytes—Sodium, Potassium, Calcium, Glucose

- May be useful to monitor serum sodium and potassium in patients with dementia due to metabolic disorders.
- Hypercalcemia with hyperparathyroidism, and metastatic bone tumors.

### TFTs

- An elevated TSH level with a low free T<sub>4</sub> level is characteristic of primary hypothyroidism.
- A decreased TSH level with a high free T<sub>4</sub> level is characteristic of primary hyperthyroidism.

### Neuroimaging — CT/MRI

- As a general rule, imaging should be performed in most patients with dementia. However, it may not be warranted in patients in whom the medical history reveals no significant findings, the results of physical and neurologic examination are normal, and the onset and progression of cognitive decline are consistent with AD.
- The choice of imaging method is determined by either the patient's condition and suspected pathologic cause at presentation or the brain region to be examined.
- CT is useful for excluding large strokes, subdural hematomas, tumor, and hydrocephalus.
- MRI is particularly recommended in patients with an atypical presentation, rapid deterioration, incontinence, focal neurologic signs, past history of head injury, or systemic diseases that prominently affect the brain (e.g. HIV infection, MS, SLE).
- New techniques including *diffusion and perfusion magnetic resonance imaging* are helpful for the differentiation between vascular dementia and degenerative disorders. *Magnetic Resonance spectroscopy* evolves as a tool for the diagnosis of different forms of degenerative dementia. *Multimodal magnetic resonance* holds promise to diagnose AD at early clinical stages and to monitor the progression of the disease.<sup>7</sup>

## INVESTIGATIONS—SPECIFIC

### Infection Screen

- Blood and urine culture may be indicated in immunocompromised patients with resistant infection.

### Vitamin B<sub>12</sub> Assay

- Vitamin B<sub>12</sub> deficiency in megaloblastic anemia, and not infrequently found with subacute combined degeneration of the cord.

### VDRL/Fluorescein Treponema Antibody (FTA-ABS)

- Neurosyphilis—VDRL test produces false-positive result; it must be followed with a sensitive FTA-ABS test.

### HIV Serology

- If the history indicates.

### ANA, Anti-ds DNA

- Connective tissue disorders, such as vasculitis.

### CSF

- May be indicated in those with following features:
  - Acute febrile episodes with meningeal signs
  - Atypical presentation (e.g. seizures; facial, ophthalmic, trigeminal cranial neuropathies)
  - Clinical findings suggestive of normal-pressure hydrocephalus
  - Evidence of immunosuppression
  - Positive serum fluorescent treponemal antibody absorption test
  - Suspected CJD (detection of specific 14-3-3 protein in CSF suggests CJD)
  - Imaging abnormalities (e.g. meningeal enhancement)
  - Cytology to exclude carcinomatous meningitis.

### CXR/ECG

- To investigate possible cardiac and pulmonary sources of cognitive dysfunction such as silent MI; consolidation due to pneumonia, SOL, or neoplasm.

### EEG

- In CJD and nonconvulsive seizure disorder

### SPECT/PET

- SPECT and PET techniques that visualize cerebral functions as glucose metabolism and

blood flow, may provide positive evidence supportive of the diagnosis of AD, and may be helpful to differentiate AD, FTD, and CJD.

### MR Angiography (MRA)

- MRA allows for examination of cerebral arterial vasculature in patients with suspected cerebrovascular disease, and
- Cerebral vasculitis is a possible cause of dementia.

### Brain and Meningeal Biopsy

- Biopsy (Bx) sampling may be helpful in the diagnostic approach to rare cases of dementia for which a reliable diagnosis cannot be established on the basis of clinical symptoms, CSF parameters, EEG, and MRI results, e.g. CJD, CNS vasculitis, and potentially treatable neoplasms or sarcoid.

### Genetic Test

- The genetic test for apolipoprotein E4 (apoE4): In general apoE4 is associated with increased risk of developing AD and other neurodegenerative disorders.

### Neuropsychologic Evaluation

- To diagnose early dementia and to rule out *pseudodementia*<sup>††</sup>. Patients with pseudodementia often have a previous history of depression or a family history of mood disorder.

<sup>††</sup> *Pseudodementia* is a term used to describe the *reversible* cognitive impairment associated with major depressive disorder in older adults. The use of this term has been disputed by some investigators who note that though severe depression can cause real cognitive impairment, the condition is treatable (unlike *irreversible* dementias such as AD). When depression is treated, many experience improvement in cognitive function, and some go on to develop dementia within 2 years; therefore, there is nothing *pseudo* about the disability resulting from severe depression. (Ref. McAllister TW. Overview: pseudodementia. Am J Psychiatry. 1983 May; 140(5):528-33. [ PMID: 6342420]).

## CLINICAL NOTES

- Before confirming dementia, rule out *benign forgetfulness of the elderly*, also known as *age-associated memory impairment*, or MCI, i.e. dementia not so progressive or serious that it impairs reasonably successful and productive daily functioning
- Dementia is diagnosed from the history and basic examination, especially cognitive testing (e.g. The Mini-Mental Scale Examination,<sup>8</sup> i.e. MMSE<sup>‡‡</sup>; St. Louis University Mental state examination, i.e. SLUMS)<sup>9</sup> and confirmed by psychometric testing (e.g. the Wechsler test and/or the Stanford-Binet Intelligence Scales)
- The MMSE is commonly used as a screening tool to detect dementia. However, it performs poorly in identifying persons with mild neurocognitive disorder. The SLUMS examination is a 30-point screening questionnaire that tests for orientation, memory, attention, and executive functions, and is possibly better at detecting mild neurocognitive disorder, which the MMSE failed to detect<sup>10</sup>
- MMSE is also been found to be biased by age and education level. Statistical data indicates that its appropriate cut-off scores can improve the sensitivity of culturally modified versions of the MMSE. A *7 minute mental screening (7MS)* tool<sup>§§</sup>, consisting of 4 brief tests (enhanced cued recall, temporal orientation, verbal fluency, and clock drawing) to distinguish between patients with probable AD and healthy control subjects appears

<sup>‡‡</sup> MMSE is only a formal screening procedure to quantify cognitive impairment; it is not diagnostic, but can be used over a period of time to follow progression of dysfunction. Further cognitive assessment is indicated in specific patients to confirm dementia.

<sup>§§</sup> Described by Solomon and colleagues, the 7 minutes screening battery takes approximately 7 to 11 minutes.

highly sensitive to AD, and may be useful in helping to make initial distinctions between patients experiencing cognitive changes related to the normal aging process, and those experiencing cognitive deficits related to dementing disorders such as AD. It has reasonable inter-rater and test-retest reliability, can be administered in a brief period, and requires no clinical judgement and minimal training.<sup>11-13</sup>

- Unless the patient has obvious and profound cognitive impairment, it is generally advisable to first interview him or her alone, followed by an interview with a close family member or caregiver (Table 12.4).<sup>14</sup>

**Table 12.4:** Questions for relatives to detect possible early dementia

- |   |
|---|
| <ul style="list-style-type: none"> <li>• Have you noticed any change in personality?</li> <li>• Have you noticed increased forgetfulness or anxiety about forgetting things (such as using lists more, etc)?</li> <li>• Have any activities been given up (hobbies and interests, shopping, dealing with finances) and why?</li> <li>• Have you noticed nocturnal confusion or muddling when out of usual routine or environment, or unusual avoidance of new circumstances?</li> <li>• Have you noticed surprising failure to recognize people (such as more distant relatives)?</li> <li>• Have you noticed undue difficulty in speech?</li> <li>• Have changes been gradual or has there been sudden worsening?</li> </ul> |
|---|
- In an elderly with suspected dementia, cognitive testing should be ideally performed after assessing their visual and hearing status. Their visual and hearing deficit may add to confusion and misinterpretation of end result, leading falsely being classified them as demented. Patients with early or doubtful dementia should be screened periodically up to six months and possibly at intervals thereafter
  - Ten early warning signs—Due to time constraint, it is difficult to perform screening test on all elderly patients coming to the office. Therefore, particular attention to the presence of warning signs suggestive of cognitive impairment is a useful adjunct to maximize the gain:
    1. Memory loss that is getting worse, e.g. cannot remember recent information, forget names and appointments;
    2. Difficulties with familiar activities, e.g. housewife to prepare a meal;
    3. Language problems, e.g. has trouble expressing thoughts, difficulty finding right words;
    4. Problems with spatial and temporal orientation, e.g. get lost at familiar place;
    5. Impaired capacity of judgement, e.g. dress inappropriately;
    6. Problems with abstract thinking, e.g. financial mistakes, simple miscalculations;
    7. Leaving things behind, losing things;
    8. Mood swings and behavioral changes, e.g. sudden mood swing without discernible cause, explosive outbursts;
    9. Personality change, e.g. a friendly person becomes unexpectedly angry, jealous; and
    10. Loss of initiative, e.g. lose interest in hobbies, excessive procrastination, failure to thrive.
  - Some of the potentially reversible causes of dementia should be considered before a diagnosis of AD is made (Table 12.2).
  - History should include drug list, head trauma, alcoholism, gastric surgery, risk factors for HIV, functional disabilities, degree of social support, and familial disorders.
  - Family history— As many as 40-50% of patients with FTD have an affected family member.
  - Drug therapy of dementia— Although some drugs have shown low risk for causing cognition disorders in research studies, risk may be increased in frail older adults taking several medications, and each case should be reviewed carefully.<sup>15</sup>
  - As cognitive decline is a feature of number of medical conditions, the physical and systemic review must be thorough and detailed. Special attention must be paid for signs of common problems at the patient's age, including:
    - Nutritional status, anemia



- Audiovisual loss
- Hygiene – oral, feet, perineum
- Physical abuse or neglect
- Issues of poor balance when standing up or walking or gait
- Localizing or lateralizing motor signs
- Signs of extrapyramidal lesion (parkinsonism)
- Other systemic disorder (metabolic syndrome<sup>16,17</sup> hypertension, hypotension,<sup>18</sup> hypothyroidism).
- Psychiatric assessment:
  - Depression in the elderly may mimic dementia, and may even coexist in a significant number of individuals (*vide supra*: pseudodementia).
  - Patients with mild HIV dementia commonly present with psychiatric symptoms of depression and anxiety. Therefore, screening all patients with HIV infection who present with depression for early HIV dementia is imperative.
- Among a long list of the differential diagnosis of dementia, four common diseases – AD, VaD, (Table 12.5), DLB, and FTD – should be considered, based on history, physical examination, and simple neuropsychological evaluation. Although depression, delirium, psychosis, aphasia, and mild cognitive impairment share some features with dementia, each is a distinct syndrome with its own differential diagnosis. It is important to consider all of these syndromes when evaluating a patient with suspected dementia.
  - AD—Memory decline is the hallmark of cognitive change in AD. In the early stage, memory impairment for recent events is common whereas long-term memory remains intact. As the disease progresses, individuals with AD are increasingly unable to recall more distant memories.
  - VaD—Typical cases are usually seen with atherosclerotic comorbidities (diabetes

**Table 12.5:** Alzheimer's disease and vascular dementia: the differential diagnosis

Type	Alzheimer's disease	Vascular dementia
Onset	Gradual	May be sudden
Progression	Steady decline	Stepwise decline
Motor system	Normal	Focal deficits typical
Neuroimaging findings	Normal or atrophy	May suggest vascular disease
Gait	Normal	May be abnormal
Comorbid illness	No causative role	Hypertension, diabetes, CHF, atrial fibrillation, IHD as precipitating causes

mellitus, hypertension, coronary heart disease, and peripheral artery disease). The onset of cognitive decline is either subtle or abrupt, and there is psychomotor slowing, executive dysfunction, focal cognitive deficits and motor signs.

- DLB—Clinical features are fluctuating cognitive impairment over weeks or months affecting memory and higher cortical functions (language, visuospatial ability such as clock drawing or copying of a complex figure, or reasoning); mild spontaneous extrapyramidal symptoms; recurrent visual hallucinations, and parkinsonism, with intervening episodic lucid interval. In terms of making a diagnosis, the two most confusing diseases are DLB and Parkinson's disease with dementia (PDD) because the clinical features are similar.
- FTD—Personality and behavioral changes (apathy, withdrawal, mutism) are predominant with less prominent memory loss early in the course; frequently FTD is misdiagnosed as personality disorders or late-onset psychiatric disorders.
- Aging affects the clinical presentation of both hypothyroidism and hyperthyroidism. Some of the classic clinical features seen in younger



patients (e.g. cold intolerance, weight gain in hypothyroidism; and tremor, nervousness, polyphagia, increased sweating in hyperthyroidism) are absent in elderly patients. Also, *apathetic hyperthyroidism* (i.e. paradoxical presentation of hyperthyroidism with fatigue, psychomotor slowing, depression, and weight gain) may also occur in this population. Moreover, the common clinical features of hypothyroidism (e.g. fatigue, constipation, cognitive loss) are often attributed to normal aging. These factors, along with the fact that hypothyroidism has an insidious onset and affects multiple organ systems, may cause considerable delay and difficulty in diagnosis. Therefore, it is important to have a high index of suspicion and a low threshold for screening for thyroid dysfunction in elderly patients who present with vague, nonspecific symptoms associated with MCI.

## RED FLAGS

- Dementia and delirium can appear in the same patient; however, it is important to distinguish dementia from delirium (acute metabolically induced state of fluctuating consciousness). Table 12.6 compares the features of delirium with those of dementia
- When dementia and delirium coexist, making it difficult to separate them clinically, it is not appropriate to give a patient a new diagnosis of dementia during a state of delirium. With serial observations as the delirium resolves, it becomes possible to differentiate them
- HIV dementia may manifest with acute-onset psychotic symptoms including delusions and hallucinations, and these patients are at a higher risk for suicidal and homicidal ideation. The initial interview should include screening for possible suicidal and homicidal ideation

**Table 12.6:** Comparison of features of delirium and dementia

Delirium	Dementia
Acute onset	Insidious onset
Profound confusion, clouding of or impaired consciousness, drowsy, anxiety, agitation, bewilderment	Clear consciousness
Perceptual abnormalities (illusions, hallucinations, imaginary conversations or activities)	Global impairment of cerebral functions (e.g. recent memory, intellectual impairment, personality, and behavior abnormalities)
Paranoid ideas/delusions; fluctuating course with lucid intervals	Progressive course
Reversible	Irreversible

- “Despite the reemergence of syphilis with the AIDS epidemic, neurosyphilis is often neglected in the differential diagnosis of patients with aseptic meningitis and mental status changes who are negative for the HIV. The high mortality rate associated with delay in recognition, diagnosis, and treatment of neurosyphilis obligates its inclusion in the differential of young patients with cognitive decline.”<sup>19</sup>
- The mere presence of cerebral atrophy on a scan should not be taken as evidence of dementing process. Atrophy can occur in individuals with no cognitive impairment.

## SELECTIVE GLOSSARY

**Normal pressure hydrocephalus—NPH** describes hydrocephalus in the absence of papilledema and with normal CSF opening pressure on lumbar puncture. The clinical symptom complex is characterized by abnormal gait, urinary incontinence, and dementia. It is an important clinical diagnosis because it is a potentially reversible cause of dementia. The features of raised intracranial pressure are generally absent. The syndrome mainly occurs in the seventh or eighth decades of life. Possible etiologic factors include head

injury, subarachnoid hemorrhage, meningitis, and CNS tumor. The most reliable marker of NPH is the characteristic *magnetic gait* in which patient has great difficulty in lifting feet off the ground while upright. This gait disorder looks like a very severe shuffling gait of PD with marked difficulty taking the first step (start hesitation) or turning. However, rigidity, tremor, and slowing of rapid, alternating movements that are common with PD are less commonly observed in NPH. Incontinence is usually urinary but may be fecal. In earlier stages, patients may complain of urgency and frequency rather than true incontinence. Dementia is characterized by prominent memory loss and bradyphrenia, i.e. slowness of thought processes. MRI assessment of CSF flow is found to be a promising technique for evaluation of patients with suspected NPH.

**Mild cognitive impairment**<sup>20-22</sup> — MCI is a syndrome defined as cognitive decline greater than expected for an individual's age (generally older than 65 years) and education level, but that does not interfere notably with activities of daily life. Several terms have been suggested to identify cognitive disorders without dementia. *Benign senescent forgetfulness*, *age-associated memory impairment* and *aging-associated cognitive decline* are considered to fall within the limits of normal aging. A recently proposed term, MCI, as opposed to the terms mentioned above, identifies a transitional state between normal aging and dementia. Some people with mild cognitive impairment seem to remain stable or return to normal over time, but more than half progress to dementia within 5 years. Mild cognitive impairment can thus be regarded as a risk state for dementia, and its identification could lead to secondary prevention by controlling risk factors such as alcoholism, smoking, obesity, systolic hypertension, etc. Recently, it has been proposed to classify mild cognitive impairment

according to memory and nonmemory involvement as amnesic, multiple domain and nonmemory single domain clinical subtypes. However, further studies are suggested to arrive at a consensus on the diagnostic criteria for MCI, determining the subgroups and its treatment modalities.

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## CHAPTER

# 13

## Diarrhea

### SYNOPSIS

The definition of *diarrhea* is somewhat controversial. It depends on the patient's as well as the physician's perspective. Scientifically, diarrhea exists if more than 200 g stool is passed daily, which is best determined by a 72-hour stool collection.<sup>1</sup>

Patients usually consider diarrhea as being an increase in the daily frequency, liquidity, or volume of the stool. Clinically, it may be defined as more than 3 bowel movements in a day. However, there may be some exceptions to this definition. Stool weight depends on dietary intake (e.g. Indian diet has high fiber content, and hence they have increased stool weight >200 g/day); therefore, stool weight by itself is an imperfect criterion to define diarrhea. Moreover, patient's understanding of 'diarrhea' varies considerably—many complain of diarrhea when their stool is loose in consistency, while others complain only when their stool frequency increases.<sup>2</sup> Therefore, a more practical definition of diarrhea may be taken as, 'too frequent passage of too fluid stools', as compared to patient's baseline pattern.

Diarrhea that lasts less than 14 days is referred to as *acute*, while *chronic* diarrhea is

defined as diarrhea that lasts for more than 4 weeks, and that often persists unless therapy is instituted (unlike acute diarrhea, which is usually self-limited). Diarrhea that lasts 14 days and resolves within a month is generally referred to as *persistent acute diarrhea*. Diarrhea is also classified into groupings such as osmotic versus secretory, infectious versus noninfectious, and inflammatory versus noninflammatory. Although each of these etiological factors is helpful for understanding the pathophysiology of individual diarrheal disease, most diarrheas are complex, and are produced by a combination of mechanisms.

Acute diarrhea is usually associated with abdominal colicky pain, urgency, tenesmus, nausea and vomiting, watery stools, with or without blood or mucus. Systemic symptoms such as fever and myalgia may be present. In severe cases of diarrhea, urgency of defecation and fecal incontinence is a common event.

In chronic diarrhea, the history is often nonspecific and physical findings are lacking. Many patients do not seek medical attention unless their diarrhea is associated with other symptoms, such as weight loss, fecal incontinence, rectal bleeding, or abdominal pain.

The majority of cases of acute diarrhea are benign and self-limiting; but in selected clinical settings such as elderly, dehydrated, immunocompromised, or patients on immunosuppressive therapy, this ailment can be life-threatening. Further, the diagnosis of functional disease in patients with chronic watery diarrhea should be performed with caution, since in most cases there is an organic cause that justifies diarrhea.<sup>3,4</sup>

The goal of the initial evaluation of an adult with diarrhea, therefore, is to differentiate benign patients from more serious or chronic disorders needing thorough investigations because of the possibility of more serious underlying disease. Although the evaluation can be taxing, making an accurate diagnosis is rewarding, because effective therapy is available for many of the conditions that cause chronic diarrhea.<sup>5</sup>

## DIFFERENTIAL DIAGNOSIS

### Common

- Infections
  - Acute (Viral: rotavirus)
  - Bacterial (*Salmonella*, *Shigella*, *S.aureus*, *Campylobacter*, traveler's diarrhea)
  - Parasitic (*Giardia*, *Entamoeba*, *Cryptosporidium*)
  - Helminthic (*Ascariasis*, *Ancylostoma duodenale*, *Trichuris trichiura*).
- Chronic (*Giardiasis*, *Amebiasis*, TB enteritis, HIV/AIDS infection)
- Food poisoning
- IBS
- Laxative abuse.

### Occasional

- Diabetic autonomic neuropathy
- Hyperthyroidism
- Fecal impaction with spurious diarrhea
- Hemorrhagic colitis (*E. coli* O157:H7: *vide infra* ↓↓)
- Pseudomembranous colitis (PMC: *vide infra* ↓↓).

### Rare

- Inflammatory bowel disease (IBD)
- Colon malignancy
- Mesenteric ischemia
- Malabsorption (lactose intolerance, tropical sprue)
- Post GI tract surgery.

## INVESTIGATIONS—GENERAL

### CBC

- Leukocytosis in invasive diarrhea or dysentery.
- Anemia may suggest blood loss, malabsorption, infection, or malignancy.
- Eosinophilia may suggest parasitic disease or allergic reaction.
- Megaloblastic anemia suggests malabsorption of B<sub>12</sub> or folic acid.

### ESR

- May be elevated in infection, IBD or malignancy.

### Blood Glucose

- To diagnose and monitor blood glucose in diabetes mellitus.

### Metabolic Panel

- Urea, creatinine elevated with hyponatremia
- Hypokalemia in dehydrated patients.

### HIV

- May be indicated in patients with chronic, persistent diarrhea.

## INVESTIGATIONS—SPECIFIC

### Fecal Leukocytes

- The presence of fecal leukocytes > 10/ (or lactoferrin) in stool suggests an inflammatory diarrheal disease and may support obtaining stool culture.

**Rectal Swab for c/s**

- Useful only if the patient has persistent fever, bloody diarrhea, immunocompromised, or occasionally in traveler's diarrhea. Routine cultures will detect *Shigella*, *Salmonella*, and *Campylobacter* species. Special media and conditions are required for pathogens such as *E. coli*-057: H, *Vibrio cholerae*, *Yersinia*, etc.

**FOBT**

- Positive fecal occult blood may indicate inflammatory, neoplastic disease, or ischemic colitis.

**Stool for Protozoa**

- Fecal ELISA test for giardia-specific antigen, cysts of *E. histolytica*, and strongyloides may be helpful.

**Stools for *Clostridium Difficile* Titer**

- Helpful if the patient is taking or has received antibiotics within the past one month and PMC is strongly suspected.

**Stool pH**

- pH <5.3 indicates carbohydrate malabsorption.

**Stool for ZN Stain (Modified)**

- For *Cryptosporidium*, *Isospora belli*, *Cyclospora* in HIV infection.

**Stool Chemical Analysis**

- Stool volume, pH, osmolality, and electrolytes estimation is useful in evaluating obscure cases of chronic diarrhea of secretory and osmotic etiology. Osmotic gap < 50 mOsm is suggestive of secretory diarrhea, and >125 mOsm is suggestive of osmotic diarrhea.

**Stool Fat (Sudan Stain)**

- If a patient is ingesting fat (>80 g per day), Sudan Test is excellent for proving clinical

suspicion of fat malabsorption (part one of the test - stool fat greater than 5 to 7 g. / 24 hr.), and it has the added advantage of being able to suggest maldigestion of dietary triglyceride (part two of the test). If both part two and part one of the Sudan Test is positive, it indicates maldigestion of dietary triglyceride (pancreatic insufficiency, small bowel resection). A negative part two of the Sudan Test does not exclude pancreatic insufficiency. Mineral oil, and the unabsorbable fat substitute, sucrose, polyester could cause false-positive Sudan Tests (parts one and two).

**TFTs**

- Low TSH with elevated T4 in thyrotoxicosis.

**LFTs**

- Raised alkaline phosphatase in metastasis; higher values of  $\gamma$ -glutamyl transferase ( $\gamma$ GT) in chronic alcoholics.

**Sigmoidoscopy with Biopsy and Culture**

- Flexible sigmoidoscopy may be useful in patients with signs and symptoms of proctitis (tenesmus, rectal pain, and rectal discharge) or *C. difficile* colitis, or for identifying noninfectious causes of bloody diarrhea such as IBD or ischemic colitis.

**Colonoscopy or Barium Enema**

- Colonoscopy is more sensitive than barium enema in detecting PMC, ischemic colitis, diverticular disease, and tumors and allows procurement of mucosal biopsies. The terminal ileum may also be inspected in most patients.

**US or CT Abdomen**

- For evidence of organomegaly, metastasis, or to know the site and extent of carcinoid syndrome.



### Upper GI Barium Series

- Most commonly used when evaluating for Crohn's disease.

### Laxative Abuse Detection

- Stool water that turns red after alkanization confirms the presence of phenolphthalein, a stimulant laxative. Urine tests are available to demonstrate the presence of aloes, senna alkaloids, and bisacodyl. Sigmoidoscopy shows *Melanosia coli* (graphically reminiscent of tiger, crocodile, or toad skin: *vide infra* ↓↓), i.e. brown discoloration to the colonic mucosa.

### Urine 24 hr Collection for 5-HIAA Excretion

- In suspected carcinoid syndrome.

### Serum Gastrin

- In Zollinger-Ellison syndrome.

### Serum Calcitonin

- To rule out medullary carcinoma of the thyroid.

## CLINICAL NOTES

- Two common conditions, usually associated with the passage of stool totaling <200 g/d, must be distinguished from true diarrhea. *Pseudo diarrhea*, or the frequent passage of small volumes of stool with rectal urgency, and accompanies irritable bowel syndrome or anorectal disorders like proctitis. *Fecal incontinence* is the involuntary discharge of rectal contents and most often caused by neuromuscular disorders or structural anorectal problems. Diarrhea and urgency, especially if severe, may aggravate or cause incontinence. Many patients are hesitant to discuss it because of embarrassment. However, it is important to ask about fecal incontinence because the condition requires further evaluation. A careful history and physical examination generally allow these conditions to be discriminated from true diarrhea
- The duration of symptoms is important in the assessment of diarrhea. While infection is the leading cause of acute diarrhea (viral or bacterial), most cases of chronic diarrhea are noninfectious—IBS being the leading cause of chronic diarrhea
- History should include recent consumption of unsanitary food or water (raw or poorly cooked foods such as eggs, meat, shellfish, dairy products, fruits and vegetables, or foods that may have been improperly handled or stored). Patients should be asked specifically about the use of public swimming pools, recent travel (ETEC infection), antibiotic use within two months (PMC), domestic animal exposure (Campylobacter infection), previous surgery (cholecystectomy, intestinal resection and surgery for peptic ulcer disease), or radiation exposure
- A careful medication history should specifically screen for antibiotic use causing PMC, illicit drugs, alcohol, antacids, and laxative abuse. In chronic diarrhea, associated medical disorders such as diabetes mellitus, dysmotility diarrhea, arthropathies in IBD are helpful in the diagnosis
- Sexual history is important, particularly if there has been oral-genital or oral-anal contact. Homosexuals (gay bowel syndrome) and HIV individuals are at a higher risk for exposure to infectious agents, and diarrhea may be the initial presenting manifestation
- Past medical history should focus on any prior history of diarrheal illness, and significant underlying medical problems (e.g. AIDS, diabetes, cirrhosis, sickle cell disease, cancer, endocrine - thyroid, Z-E syndrome, or autoimmune disease), prior radiotherapy, and immunological status.

- Important features in the history which help guiding the evaluation and management of patients with acute diarrhea are:
  - Stool characteristics—frequency, consistency, quantity, bloody, bloody, mucus-filled, purulent, or greasy;
  - Presence of dysentery—fever, tenesmus, blood, mucus, or both;
  - Symptoms of dehydration—thirst, lethargy, postural giddiness, decreased urination; and
  - Presence of associated symptoms—nausea, vomiting, abdominal cramps, and significant upper or lower gastrointestinal bleeding (coffee ground emesis, hematemesis, melena, hematochezia).
- Some typical features of diarrhea and stools associated with common diseases are:
  - Nocturnal diarrhea—autonomic neuropathy, e.g. diabetes mellitus;
  - Diarrhea alternating with constipation - TB abdomen, laxative abuse, diverticulosis, carcinoma of colon;
  - Chronic bloody or melanotic stools with weight loss - IBD, colonic malignancy;
  - Pale, bulky, greasy, frothy, foul-smelling stools, which float in toilet, and associated with nutritional deficiency, weight loss - malabsorption syndrome; and
  - Diarrhea worsened by eating fatty foods - steatorrhea.
- The Manning criteria (Table 13.1) are helpful to differentiate IBS from organic causes of diarrhea
- Table 13.2 illustrates common findings on physical examination and their significance in patients with diarrhea.

## RED FLAGS

- Infection with *E. coli* O157: H7 presents with many clinical manifestations and should be included in the differential diagnosis for any

**Table 13.1:** The Manning criteria to distinguish IBS from organic disease

1. Onset of pain associated with more frequent bowel movements
2. Onset of pain associated with looser bowel movements
3. Pain relieved by defecation
4. Visible abdominal bloating
5. Subjective sensation of incomplete evacuation more than 25% of the time
6. Mucorrhea more than 25% of the time

**Table 13.2:** Physical signs in diarrhea

Physical signs	Significance
General exam—Fever, weight loss, tachycardia, tremor, lymphadenopathy	Infection, IBD Alcohol abuse, hyperthyroidism TB, malignancy
Skin — Erythema nodosum, dermatitis herpetiformis, flushing, venous telangiectasis, hyperpigmentation	IBD Celiac sprue Carcinoid syndrome Carcinoid syndrome Addison's disease, Peutz-Jeghers syndrome
Kaposi sarcoma	AIDS
Punch' purpura	Amyloidosis
Eyes—Iritis, uveitis	IBD
Neck—Goiter	Hyperthyroidism
Lungs—Bronchospasm	Carcinoid syndrome
Abdomen—mass, RLQ mass	Crohn's disease Colonic ischemia
Bruit	
PR—Rectal fistula, painless fissure, perianal abscess	Crohn's disease

patient with new-onset bloody diarrhea. Development of the hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) should raise strong suspicion of *E. coli* O157:H7 infection and should lead to prompt evaluation

- Nocturnal diarrhea, unless occurring in a known diabetic patient, usually points to an organic cause
- Abdominal TB (intestinal or peritoneal) can mimic IBS and must be considered in chronic diarrheal disease, especially due to rising HIV incidence

- In general, a patient with any of the following warrants thorough work up:
  - Symptoms of dehydration: Particularly postural giddiness, diminished urine output, and excessive thirst;
  - Advanced age ( $\geq 70$  years);
  - Clinically suspected neoplasm, carcinoid syndrome, colonic ischemia;
  - Compromised immune system; and
  - Inflammatory diarrhea: fever, blood and mucus in stools.

## SELECTIVE GLOSSARY

**Hemorrhagic colitis (*E. coli* O157:H7)**— Enterohemorrhagic *E. coli* (EHEC) strain designated *E. coli* O157:H7 serotype, causing Hemorrhagic colitis, is a gram-negative rod-shaped bacterium, capable of producing potent toxins [verotoxin (VT), shiga-like toxin] that cause severe damage to the lining of the intestine. Undercooked or raw hamburger (ground beef) has been implicated in many of the documented outbreaks, however, *E. coli* O157:H7 outbreaks have implicated alfalfa sprouts, unpasteurized fruit juices, milk, dry-cured salami, lettuce, game meat, and cheese curds. The illness is characterized by severe cramping abdominal pain, and diarrhea which is initially watery but becomes grossly bloody. Occasionally vomiting occurs. Fever is either low-grade or absent. The illness is usually self-limited and lasts for an average of 8 days. The majority of infections resolve completely; some victims, particularly the very young, have developed HUS, characterized by renal failure and hemolytic anemia. In the elderly, it may be complicated by TTP with high mortality rate. Because person-to-person transmission of *E. coli* O157:H7 is not uncommon, and infection with this organism may cause severe disease, stool specimens from all patients with a history of acute bloody diarrhea should be cultured for *E. coli* O157:H7.

**Melanositis coli**—It is a pigmentation of the rectal and colonic mucosa due to use (or abuse) of anthraquinone type laxatives, and occurs because of the deposition of a brown black pigment called lipofuscin in the lamina propria of the colon. The initial event is mucosal cell death or apoptosis resulting from anthraquinone laxative abuse. These cells are then phagocytosed by macrophages in lamina propria producing lipofuscin, which gives a dark color to the colonic mucosa. Its incidence is understandably higher in older population and people who suffer from conditions like IBS and chronic constipation, and is rising because of the popularity of the herbal remedies containing anthraquinone. *Melanositis coli* is a benign reversible condition with no malignant potential. The main importance of diagnosing *Melanositis coli* correctly lies in the fact that if it's extensive, there may be difficulty in differentiating it from ischemic colitis. Withdrawal of the offending laxative, which nearly always can be substituted with a bulk laxative, is sufficient treatment.

**Peutz-Jeghers Syndrome** (Pronunciation: pütz jã'gěrz)—It is a hereditary disease caused by autosomal dominant mutations involving Chromosome 19. It is characterized by the presence of intestinal polyps, consistently in the jejunum, and mucocutaneous pigmentation with melanin spots (small, flat, brown or dark blue spots with an appearance of freckles) of the lips, buccal mucosa, and digits. Isolated melanotic mucocutaneous pigmentation without gastrointestinal polyps has also been described because of the genetic variability of the syndrome. History includes:

- Family history of Peutz-Jeghers syndrome
- Repeated bouts of abdominal pain in patients younger than 25 years
- Unexplained intestinal bleeding in a young patient

- Prolapse of tissue from the rectum
- Menstrual irregularities in females (due to hyperestrogenism from sex cord tumors with annular tubules)
- Gynecomastia in males (possible due to the production of estrogens from Sertoli cell testicular tumors)
- Precocious puberty
- Gastrointestinal intussusception with bowel obstruction.

The risk of cancer remains elevated with disregard to the presence or the absence, as well as the number, of gastrointestinal polyps.

**Pseudomembranous colitis**—PMC is a descriptive term for colitides associated with pseudo-membrane formation (or plaques) on the colonic or small intestinal mucosa. Although small intestine can be involved in PMC, most cases encountered in the modern era involve only the colon. *Clostridium difficile* infection is responsible for virtually all cases of PMC; the basic mechanism in its pathogenesis being overgrowth of *C. difficile* and toxin production (toxin A is an enterotoxin, while toxin B is a cytotoxin) by the organism that causes a wide spectrum of illnesses, ranging from mild diarrhea to life-threatening PMC. The anaerobes that are normally present in the colon control colonization by *C. difficile*; therefore, antibiotics that are most active against anaerobic organisms are more commonly associated with PMC. Although clindamycin and lincomycin classically have been linked to PMC, virtually all antibiotics can cause PMC; its onset being within days after initiation of

antibiotic therapy, or can occur up to 6 weeks after discontinuation. Other causative factors for PMC are abdominal surgery, colonic obstruction, uremia, and prolonged hypotension causing hypoperfusion of the bowel. PMC also has been described with lymphoma, leukemias, and advanced HIV infection. Diagnosis is primarily by the detection of *C. difficile*, or its toxins in stool by ELISA techniques, or direct culture of *C. difficile* from the stool. CT scanning of the abdomen can be helpful by revealing the presence of bowel wall edema (>4 mm) and inflammation, particularly in cases involving the right colon. Although these findings are nonspecific, imaging studies are helpful in patients with severe disease in detecting complications (e.g. toxic dilation, perforation).

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## CHAPTER

# 14

## Dyspepsia

### SYNOPSIS

*Dyspepsia* has been said to be ill-defined, poorly defined, defying definition, and vague and misunderstood.<sup>1,2</sup> The Rome III committee recommends the following pragmatic definition of dyspepsia: “dyspepsia is defined as the presence of one or more dyspepsia symptoms that is considered to originate from the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to explain the symptoms”.<sup>3,4</sup>

It further states that the term *functional dyspepsia* should preferably be replaced by more distinctively defined disorders: (1) meal-induced dyspeptic symptoms (postprandial distress syndrome), and (2) epigastric pain syndrome. However, the committee recommends this definition particularly for research purposes.<sup>5,6</sup>

A working definition of dyspepsia may be considered as episodic or persistent upper abdominal symptoms believed to arise from the upper digestive tract (i.e. epigastrium; pain in the right or left hypochondrium is not considered to constitute dyspepsia), which may or may not be related to eating, and may include epigastric pain, bloating, fullness, belching,

nausea or early satiety. Patients use this term variously to express a feeling of bloating, burping, heartburn (pyrosis), regurgitation, early satiety, acidity, and indigestion or ‘upset stomach’. It is often accompanied by anorexia, nausea, vomiting, or flatulence. Although these symptoms are imprecise and nonspecific, care in taking the clinical history will often facilitate making a tentative diagnosis and limit unnecessary investigations.<sup>7</sup>

The main concern of the physician is to allay patient’s fear of organic GI disease by standard work up, and emphasize ‘patient empowerment’, i.e. discuss and agree with the patient how best he/she can control their symptoms with treatments available, and advise when symptoms need further investigations to rule out a more serious underlying cause.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Indiscriminate eating behavior\* (too much, too rich, too fast).

\* A rare cause of indiscriminate eating (hyperoral) behavior is *frontotemporal dementia* – vide *infra* ↓↓.

- Functional dyspepsia (Nonulcer dyspepsia, i.e. NUD<sup>†</sup>, aerophagy, IBS)
- Peptic ulcer disease (PUD<sup>‡</sup> e.g. duodenal ulcer, gastric ulcer, stress ulcer)
- GERD
- Medications (NSAIDs, iron supplements, oral antibiotics, corticosteroids, theophylline, digitalis, potassium chloride, bisphosphonates, metformin, acarbose, OTC agents/herbal-garlic, ginkgo, Saw palmetto)
- Substance use/abuse—(alcohol, tobacco, caffeine)
- Systemic disease—(IHD, viral hepatitis A infection, tuberculosis, sepsis)
- Parasites (intestinal amoebiasis, giardiasis, strongyloides)
- Psychogenic (anxiety, depression, somatization)
- Pregnancy.
- Pancreatic malignancy
- Intra-abdominal malignancy
- Gastrinoma (Zollinger-Ellison syndrome, i.e. ZES: *vide infra* ↓↓)
- Metabolic (hypercalcemia)
- Carbohydrate malabsorption (lactose, fructose).

## INVESTIGATIONS—GENERAL

### CBC

- Leukocytosis with infection (cholecystitis, pancreatitis, MI)
- IDA due to chronic GI bleeding
- Megaloblastic anemia in malabsorption and gastric carcinoma.

### ESR

- Elevated in infection, malignancy.

### FOBT and Parasites

- To screen for GI carcinoma, adenoma, intestinal ischemia, and IBD
- Stool microscopy/ELISA for parasites.

### ECG

- If coronary ischemia is likely.

### Metabolic Panel

- Electrolytes, urea, creatinine, glucose, and calcium.

### TFTs

- Performed to evaluate for hypothyroidism or hyperthyroidism.

### LFTs, Amylase, Lipase

- Performed to check for pancreatic or obstructive biliary disease.

### Occasional

- Coronary ischemia
- Gastroparesis (diabetes mellitus, vagotomy)
- Hepatobiliary disease (cholecystitis, cholelithiasis)
- Pancreatitis (chronic)
- Organ failure (cardiac, renal, hepatic)
- Upper GI malignancy (esophagus, gastric).

### Rare

- Ischemic bowel disease
- Hepatobiliary neoplasms (primary, secondaries).

<sup>†</sup> The older synonym *nonulcer dyspepsia*, though still widely used, is not recommended because some of the patients have symptoms typical of ulcer disease while others have symptoms not at all like an ulcer. Furthermore, peptic ulcer is not the only organic disease to be excluded before the diagnosis of functional dyspepsia is appropriate. (Ref. - Dyspepsia-A National Clinical Guidelines, Scottish Intercollegiate Guidelines Network; March 2003).

<sup>‡</sup> PUD includes ulcer in the stomach, pylorus, duodenum, or a Meckel's diverticulum, as well as ulcers at sites of GI anastomosis (stomal ulcer) and at the gastroesophageal junction.



## INVESTIGATIONS—SPECIFIC

### EGD with or without Biopsy for *H. Pylori* (HP)

- Endoscopy is indicated in:
  - All patients with dyspepsia aged >45 years;
  - In younger patients with positive HP serology, or urea breath test (UBT);
  - Presence of any 'alarm' features (see 'red flags' below);
  - History of ulcerogenic medications; and
  - To obtain biopsy (Bx) specimens, particularly of gastric ulcer.

### Tests for HP

- These can be either noninvasive (serology, UBT, or stool antigen test), or invasive (histology, and rapid urease test)
- *IgG serology* is easy and most suitable for initial diagnosis of HP infection because of its easy availability and low cost; but a positive test only indicates an ongoing or previous exposure to HP, and not active infection. Therefore, this test is not useful for confirming eradication of the organism, and documenting successful treatment
- With the *UBT*, if HP is present, the urease produced by the organism breaks down ingested carbon 14 labelled ( $^{14}\text{C}$ ) urea into ammonia and labeled carbon dioxide, which can be detected in the patient's breath. UBTs are useful both for diagnosing active infection and confirming eradication following treatment with antibiotics, because once HP is eradicated, urease is no longer produced. The UBT is more sensitive and specific than serology testing, but its disadvantage is that it requires  $^{14}\text{C}$  (or  $^{13}\text{C}$ ) detection equipment and tends to be more expensive
- *Stool antigen test* (PCR for HP), like UBT, is useful both for diagnosing active infection

and confirming eradication following therapy. It is inexpensive and the test of choice, especially in children

- *Histology*: Mucosal biopsies (four—two antral, and two corpus) obtained during endoscopy can be stained (H&E, Giemsa, or Genta stains) to identify HP
- In *rapid urease test*, the tissue specimen (obtained at the time of endoscopy) is placed in urea rich agar medium with a pH sensitive dye. A color change represents a positive test
- *Culture* of HP is not often considered as diagnostic tool due to the difficulty in culturing this fastidious organism; it is mostly confined to research laboratories
- Urine and saliva tests for HP have not yet been completely validated.

### US Abdomen or CT

- Used as indicated to identify lesions that may be responsible for dyspeptic symptoms.
- Gallstones detected are usually not causative of dyspepsia.

### Esophagography and Upper GI Barium Meal Series

- Indicated if endoscopy is difficult or impossible as in patients with altered esophagogastric anatomy. A good barium meal study will identify motility disorders of the esophagus, (esophageal dilatation, loss of esophageal peristalsis, poor esophageal emptying, and 'birds beak' tapering of the distal esophagus), which may be missed endoscopically.

### Esophageal Manometry

- Not routinely used for mild to moderate symptoms because findings seldom influence further medical management; may be essential for patients who are undergoing surgery for GERD.

### 24-hour Esophageal pH Manometry

- Performed in patients who have unexplained chest pain that does not respond to medications.

### Fasting Serum Gastrin

- In patients with gastrin secreting multiple neuroendocrine tumors (MNE: *vide infra*↓↓) such as Zollinger-Ellison syndrome.

## CLINICAL NOTES

- Dyspepsia for which an underlying disease process is thought to be responsible for the symptoms is described as *organic dyspepsia*, e.g. PUD, esophagitis; when symptoms persist for more than 12 weeks, and for which no cause (structural or biochemical) can be found after investigation, is usually termed as *functional dyspepsia*—this entity is synonymously termed as NUD. The Rome III criteria for functional dyspepsia are stated in Table 14.1. However, according to the Rome III criteria, frequent clinical overlap of functional dyspepsia with IBS and GERD is very common; but this overlap does not exclude a diagnosis of functional dyspepsia.<sup>8-11</sup>

**Table 14.1:** The Rome III diagnostic criteria for Functional dyspepsia

At least 3 months (which need not be consecutive), with onset at least 6 months previously, of 1 or more of the following:
<ul style="list-style-type: none"> <li>• Bothersome postprandial fullness</li> <li>• Early satiation</li> <li>• Epigastric pain</li> <li>• Epigastric burning</li> <li>• No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms.</li> </ul>

- The investigation of choice to make the diagnosis of NUD (functional) is endoscopy of the upper GI tract. As such NUD can be referred to as investigated dyspepsia, which should be distinguished from uninvestigated dyspepsia.<sup>12</sup>

- Categorizing NUD in the diagnostic subgroups such as ulcer-like, reflux-like, dysmotility-like, and nonspecific dyspepsia have not shown to be helpful in predicting diagnosis or response to treatment. This is mainly due to large amount of overlap between types of dyspeptic symptoms for patients with underlying gastric ulcer, duodenal ulcer, GERD, or NUD, which makes the clinical history of little use in directing therapy toward a specific disease state.<sup>13,14</sup>

However, careful history is important to:

- Elicit classical symptoms of specific disorders, e.g. PUD, cholecystitis, GERD;
- Detect *complicated* ulcer disease, e.g. IDA due to chronic GI blood loss, vomiting due to gastric or duodenal outlet obstruction, sudden, severe abdominal pain due to peptic perforation;
- Elicit *alarm* symptoms (see below) that suggest a high probability of organic disease, and need further testing rather than empiric therapy; and
- Detect *atypical* symptoms more suggestive of other disorders, e.g. MI, IBS.
- History should also include a complete review of medications and OTC agents (see above); dosage reduction or discontinuation of the offending agent may relieve patient's symptoms and avoid further expensive work-up
- Patient's habits (alcohol, smoking), lifestyle, past history of surgical procedures (appendicectomy, gastrectomy), etc. may suggest potential etiologies
- Evaluation of psychosocial factors—The contribution of psychosocial factors to the illness, i.e. functional dyspepsia, and the decision for psychological referral can be evaluated through several questions during the first visit. For example:
  - What is the patient's understanding of the illness? Simple questions such as, "what do you think is causing your symptoms?",

or “is there anything that you are worried about regarding these symptoms?”, may help elicit concerns, relieve worries, and improve patient satisfaction.

- Does the patient accept stressful lifestyle and/or stressful life events playing a contributing role?
- Is there a concurrent psychiatric diagnosis such as anxiety, depression, somatization, alcoholism, and drug dependency?
- What is the family’s involvement in terms of emotional and moral support? When healthy and supportive behaviors are present, the family members can be recruited to help the patient toward recovery; or else counseling may be indicated.
- Unless the clinical data (e.g. occult blood in the stool, significant weight loss, or abnormal physical findings) suggest the possibility of other disorders, the diagnostic studies ordered on the first visit should be limited. The choice depends on the nature and severity of symptoms and associated clinical factors (see below - alarm signs and symptoms). However, in the majority of patients with functional dyspepsia, wherein a variety of emerging therapies are being developed, but unfortunately, to date, all of these therapies have yielded only marginal results. Therefore, the physician’s most effective approach is to maximize the physician-patient relationship to help them cope with their symptoms.<sup>15</sup>

## RED FLAGS

- It is prudent to consider any dyspeptic symptoms as IHD, especially under following circumstances:

- Any associated chest pain, dyspnea, or sweating
- Pain radiation to arm, jaw, shoulder, back
- Associated with dizziness, syncope, or transient mental status changes
- History of IHD or cardiac risk factors
- Pulse and blood pressure abnormality.
- *Alarm* symptoms and signs suggestive of organic cause in dyspeptic patients, and in whom endoscopy is indicated, irrespective of their age, include:
  - Progressive unintentional weight loss > 3 kg (malignancy)
  - Constant or severe abdominal pain, nocturnal pain (malignancy)
  - Pain that radiates to the back (posteriorly located ulcer, pancreatitis)
  - Persistent heartburn, regurgitation, vomiting (obstruction)
  - Hematemesis, melena, anemia (chronic GI bleeding)
  - Progressive difficulty in swallowing (esophageal lesion)
  - Jaundice (alcoholic liver disease, metastasis)
  - Epigastric mass or suspicious barium meal
  - Unresponsive to the sequential treatments for *H. pylori* eradication
  - Previous peptic ulcer
  - Family history of cancer.

## SELECTIVE GLOSSARY

**Frontotemporal dementia (FTD)**— It is a group of diseases in which parts of the brain (the frontal and temporal lobes) shrink, or atrophy, causing changes in personality and behavior.

People with FTD may have:

- Loss of social component—Not express any caring for others.

- Loss of personal awareness—Not attend to personal hygiene
- Disinhibition—Say rude things to others, expose themselves, or make sexually explicit comments, or exhibit other socially inappropriate behavior
- Hyperorality—Excessive eating, be obsessed with repetitive routines or develop unusual food obsessions, such as eating the same kind of food or eating in the same restaurant repeatedly
- Speech output change—Reduction of speech, stereotype of speech, and echolalia, difficulty understanding words and naming objects.

The physical examination usually reveals early prominent primitive or frontal reflexes. One-half of patients have a family history of dementia in a first-degree relative. There are three principal varieties of FTD: frontal variant FTD, semantic dementia, and progressive nonfluent aphasia. Frequently, FTD is misdiagnosed as personality disorders or late-onset psychiatric disorders.

**Multiple Endocrine Neoplasias (MENS)**—MEN syndromes are genetic neoplastic conditions in which two or more endocrine glands develop hyperplasia, adenoma, or carcinoma, concurrently or consecutively. Two of the types that occur are well-documented: *MEN 1 (Werner's syndrome)* involves hyperplasia and adenomatosis of the pituitary and parathyroid glands, islet cells of the pancreas and, rarely, the thyroid and adrenal glands; *MEN 2 (Sipple's syndrome)* which has three variants, classified as *MEN2A*, *MEN2B* and involves medullary carcinoma of the thyroid, with hyperplasia and adenomatosis of the adrenal medulla (pheochromocytoma) and parathyroid glands. *MEN 1* is the most common form, characterized by the combined occurrence of tumors in the parathyroid glands, the pituitary gland, and the pancreatic islets. The resulting clinical signs

include hyperparathyroidism, hypercalcemia, hyperprolactinemia, Cushing's disease, gastrinoma, and Zollinger-Ellison syndrome. This disease is due to loss-of-function of the *MEN1* gene, a tumor suppressor gene on chromosome 11 (Locus: 11q13). Diagnosis of *MEN1* depends on having a high level of suspicion in patients who present with one of the features such as recurrent ulcers at atypical sites (esophagus, jejunum) with poor response to standard ulcer therapy, hyperparathyroidism, or increased gastric acid secretion, and serum hypercalcemia. Many people may also be diagnosed because of a proband in the family.

**Zollinger-Ellison syndrome**—A syndrome that is characterized pathophysiologically by a significant hypergastrinemia derived from a gastrin-secreting neuroendocrine tumor with a primary location in the pancreas or duodenum, but also found at other anatomic sites, (e.g. heart, ovary, gallbladder, liver, kidney), including stomach and small intestine (gastrinoma), which sometimes occurs in families with *MEN-1*. Chronic hypergastrinemia triggers gastric acid hypersecretion yielding in chronic or recurrent or refractory peptic ulcer disease and/or chronic diarrhea. One half of patients with ZES will have distant metastases in the liver by the time the diagnosis is established and one half of all patients with ZES will experience chronic diarrhea as chief complaint rather than peptic ulcer-related symptoms and signs. Therefore, a high index of clinical awareness is needed to make a diagnosis of ZES. The combination of diarrhea and abdominal pain is present in more than half the patients, usually > 40 years age. Heartburn is the third most common symptom, and this symptom mimics GERD. The other factors that alert one to the presence of underlying gastrinomas are the following:<sup>16</sup>

- Ulcers that is refractory to standard therapy
- Multiple ulcers
- Giant ulcers, larger than 2 cm
- Recurrent ulcers
- Ulcers with unexplained diarrhea
- Strong family history of ulcers
- Hypercalcemia
- Duodenal ulcer that is not related to *Helicobacter pylori* infection or nonsteroidal anti-inflammatory drug use.

A family history of nephrolithiasis, hyperparathyroidism, and gastrinoma also may be present. Fasting serum gastrin (serial measurements on different days) is the best single screening test. To localize the gastrin-secreting tumor, computer-assisted tomography, endoscopic ultrasound, and somatostatin receptor scintigraphy provide useful help; but most recently endoscopic ultrasound with high resolution transducers appear to improve preoperative site localization.

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## CHAPTER

# 15

## Dysphagia

### SYNOPSIS

*Dysphagia* is defined as the nonpainful subjective sensation of having difficulty in swallowing, involving any structures of the upper gastrointestinal tract—from the lips to the lower esophageal sphincter (LES). The term is used to describe disorders associated with voluntary swallowing mechanism, and also the sensation that swallowed bolus is delayed or completely obstructed in its passage to the stomach. Some of the ways patients commonly describe these feelings are—food being stuck in the throat, or retrosternally, and sometimes difficulty initiating a swallow itself. Associated symptoms such as difficult mastication, lump, fullness, or pressure in the throat or neck (*globus*), drooling, coughing while eating, change in the voice, heartburn (pyrosis), and weight loss may be present.

Dysphagia is usually divided into *oropharyngeal* and *esophageal* causes (Table 15.1). Dysphagia of oropharyngeal disease occurs in disorders proximal to the esophagus, most often of neurological or muscular origin. The patient finds difficulty in preparing and swallowing food bolus from the mouth to the proximal esophagus (*transfer*

**Table 15.1:** Dysphagia—Classification and clinical features

Oropharyngeal	Esophageal
<ul style="list-style-type: none"> <li>• Usually bolus sticking above suprasternal notch</li> <li>• Rapid onset (&lt; 2 sec)</li> <li>• Oral and/or pharyngeal symptoms are common. For example: <ul style="list-style-type: none"> <li>– Difficulty initiating a swallow</li> <li>– Slow eating</li> <li>– Nasopharyngeal regurgitation</li> <li>– Drooling of saliva (sialorrhea)</li> <li>– Change in voice or speech</li> <li>– Coughing or choking before, during, or after swallowing</li> <li>– Throat secretions, frequent throat irritation</li> </ul> </li> <li>• Risk groups: <ul style="list-style-type: none"> <li>– Any age group</li> <li>– Cerebral palsy, developmental delay</li> <li>– Patients with history of CVA</li> <li>– Immunosuppressed/immunodeficient patients</li> <li>– Ventilator-dependent patients</li> <li>– Head and neck surgery</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Usually bolus sticking below suprasternal notch</li> <li>• Slower onset (&gt; 2 sec)</li> <li>• Oral/pharyngeal symptoms are minimal or absent; esophageal or systemic symptoms may include: <ul style="list-style-type: none"> <li>– Sensation of food sticking throat/chest</li> <li>– Anorexia</li> <li>– Change in dietary habits</li> <li>– Unexplained weight loss</li> <li>– Cough</li> <li>– Chest pain</li> <li>– Odynophagia</li> <li>– Reflux of food/bile into the mouth</li> </ul> </li> <li>• Risk groups: <ul style="list-style-type: none"> <li>– Elderly</li> <li>– Diabetes mellitus</li> <li>– Immunosuppressed/immunodeficient patients</li> <li>– Patients with reflux disease</li> <li>– Alcohol, tobacco abuse</li> <li>– Myopathy, dermatomyositis</li> <li>– Ventilator-dependent patients</li> <li>– Cardiothoracic surgery</li> </ul> </li> </ul>



*dysphagia*). There may be instant regurgitation of food through the nose, choking, repetitive swallowing, or cough due to tracheal aspiration. There may also be dysphonia, dysarthria, or other neurological symptoms.

Esophageal dysphagia is difficulty in transporting food bolus down the esophagus (*transit dysphagia*), usually as a result of obstructive or motility disorders. Patients complain of food sticking at some point in esophagus, usually lower sternum or epigastrium. Patients find that they must chew their food thoroughly and that fluids may be required to ‘wash the food down’. The time taken to eat is frequently prolonged. Occasionally the patient may notice regurgitation of undigested food occurring minutes to hours after a meal.

Dysphagia should be distinguished from *odynophagia*, i.e. painful swallowing; however, it may be associated with dysphagia *per se*. In addition, dysphagia should not be confused with *globus*\*,<sup>1</sup> i.e. constant or intermittent sensation of a lump in the throat, although no organic defect is apparent.

Complaints of dysphagia are common, especially in aging persons, but many do not necessarily disclose this symptom to their physician, and for other patients swallowing impairment does not seem to be a worry.<sup>2</sup> However, in such patients with dysphagia, additional testing may be indicated to diagnose the problem and prevent complications. Therefore, although patients’ concern and experience of frequency, duration, and life interference are critical variables in consulting their physician for complaints of swallowing impairment, it is prudent for the physicians to remain alert to the presence of dysphagia in their patients.

## DIFFERENTIAL DIAGNOSIS

These may be grouped into the two broad categories as stated above:

\* Originally called ‘globus hystericus’; however, the term ‘globus’ is preferred since there is no evidence to support the occurrence of ‘hysteria’ with this condition.

## A—Oropharyngeal Causes

### Common

- Oral ulcers (aphthous ulcer; viral ulcers, e.g. HSV, CMV, HIV)
- Oral inflammatory lesions (glossitis, stomatitis, tonsillitis, ‘kissing’ tonsils, peritonsillar abscess, i.e. Quincke, epiglottitis, pharyngitis, retropharyngeal abscess, Vincent’s infection, thrush)
- Stroke (hemispheric stroke, brainstem stroke, Wallenberg syndrome, i.e. lateral medullary syndrome: *vide infra* ↓↓)
- Advanced age-related oral disorders<sup>†</sup> (loose, unhygienic, or structurally defective dentures<sup>‡</sup>, denture-induced stomatitis)
- Functional GI disorders (FGIDs: associated with IBS, anorexia nervosa)
- Dementia.

### Occasional

- Medication side-effect (xerostomia due to antihistamines, anticholinergics, antihypertensives)
- Hypopharyngeal diverticulum (Zenker’s diverticulum: *vide infra* ↓↓).

### Rare

- Premalignant lesion (leukoplakia, lichen planus)
- Neurologic disorders (PD, MS, MG, brainstem tumors)
- Degenerative motor neuron disease (bulbar palsy, pseudobulbar palsy, ALS, i.e. amyotrophic lateral sclerosis: *vide infra* ↓↓)
- Degenerative cervical spine disease (impinging cervical osteophytes)
- Oropharyngeal tumors
- Autoimmune and rheumatologic disorders (RA, scleroderma, SS, i.e. Sjögren’s syndrome: *vide infra* ↓↓, myopathies)

<sup>†</sup> Dysphagia as a result of healthy ageing is termed *primary presbyphagia*

<sup>‡</sup> *Portcullis signs*, i.e. the top denture falling on to the bottom one when the mouth is opened.

- Tracheostomy
- Psychiatric disorder (somatization)
- Infections (Polio, diphtheria, tetanus, rabies<sup>§</sup>).

## B—Esophageal Causes

### Common

- Food-bolus obstruction
- GERD
- Hiatal hernia
- Pill-induced esophagitis (NSAIDs, iron supplements, alendronate, potassium chloride, doxycycline, zidovudine)
- Functional GI disorders (FGIDs — associated with IBS, anorexia nervosa).

### Occasional

- Eosinophilic esophagitis<sup>3</sup> (*vide infra* ↓↓)
- Esophageal motility disorders, i.e. EMDs (achalasia cardia, diffuse esophageal spasm, i.e. DES, LES dysfunction, ‘Nutcracker’\*\* esophagus, i.e. NE)
- Esophageal webs, rings (Schatzki ring: *vide infra* ↓↓)
- Benign strictures (due to chronic acid-peptic ulceration)
- Benign neoplasm (leiomyoma, squamous cell papilloma)
- Infectious esophagitis (bacterial, TB, viral, fungal in immunosuppressed patient)
- Premalignant lesion (Barrett’s esophagus, i.e. BE: *vide infra* ↓↓).

### Rare

- Foreign body
- Plummer-Vinson syndrome (i.e. P-V syndrome, or Paterson-Brown-Kelly syndrome)

<sup>§</sup>In tetanus, rabies, and pharyngeal paralysis there is morbid fear of swallowing, and refusal to swallow due to fear of aspiration; this is known as *Phagophobia*.

\*\*The term “nutcracker esophagus” comes from the finding of increased pressures during contractions (when pressures exceed 180 mmHg) in the lower esophagus; a force so strong that some observers have described them to a mechanical device called *nutcracker* — a tool powerful enough to crack open a walnut or similar hard substances.

- Extrinsic compression (mediastinal mass, pericardial effusion, enlarged left atrium, thyromegaly, aortic aneurysm, dysphagia lusoria *vide infra* ↓↓)
- Neurologic disorders (CVD, PD, MS, Guillain-Barré syndrome)
- Autoimmune disorders (systemic sclerosis, or scleroderma: *vide infra* ↓↓)
- Malignant lesions (adenocarcinoma, squamous cell carcinoma, leiomyosarcoma)
- Psychiatric disorder (somatization)
- Idiopathic (or primary) achalasia.<sup>4</sup>

## INVESTIGATIONS—GENERAL

### CBC, ESR

- Reduced Hb with chronic infections, and malignancy. Anemia may be associated with P-V syndrome.
- Elevated ESR in malignancy and autoimmune disease.

### CXR

- For evidence of aspiration pneumonia, hilar lymphadenopathy, growth, aortic aneurysm, cardiomegaly (enlarged left atrium, pericardial effusion), and for locating swallowed radiopaque foreign body.

### X-ray Neck-lateral view

- For evidence of cervical osteophytes or any soft tissue lesion of retropharyngeal or postcricoid space (e.g. bacterial/tubercular abscess, metastatic lymphadenopathy) causing dysphagia.

## INVESTIGATIONS—SPECIFIC

### Barium Swallow (Barium Esophagography, or Modified Barium Swallow (MBS))

- The initial investigation of choice in patients especially with disorders of motor or ‘transfer’ dysphagia. Diagnostic features are seen in patients with esophageal webs and rings; pharyngeal pouch or diverticulum;

strictures — benign (smooth) or malignant (irregular and tortuous ‘rat-tail’ deformity); esophageal dysmotility or spasm (‘corkscrew’ deformity); achalasia cardia (‘bird’s beak’ deformity with dilated proximal esophagus, and air-fluid level); hiatus hernia; and dysphagia due to external compression such as mediastinal growth or aortic aneurysm. It also reduces the risk of endoscopic perforation in these disorders, especially in those having pouch or diverticulum. Different consistencies of barium (solid, semisolid, or liquid; barium pill, or a standard marshmallow) further assess swallowing disorders, as delays in transport may not be apparent with simple liquid barium. If the patient has noted a problem with a specific solid food, a mixture barium paste plus the offending food may provide definitive information.<sup>5</sup> The disadvantage of barium X-rays is that they are relatively insensitive in detecting mucosal disease, even if air contrast technique is added. Fluoroscopy can detect GERD.

### EGD

- Fiberoptic endoscopy directly visualizes the esophageal mucosa as well as other areas of the upper GI tract. Its direct view is superior to barium X-rays for assessing mucosal disease of the esophagus, and the esophagoscope permits assessment of structural lesions that are identified. Furthermore, punch biopsies and/or brush cytology of specific lesions are easily obtained through the endoscope. Microscopic evidence of esophagitis may be found even when the mucosa looks grossly normal
- Endoscopy is the single most useful test in the evaluation of patients with reflux symptoms, as it permits one to establish the presence or absence of esophagitis or Barrett’s esophagus. Endoscopy gives little reliable information regarding esophageal

function. However, patients with mass lesion or other lesions identified by barium swallow should undergo EGD with cytology and biopsy(Bx) to confirm the diagnosis

- EGD allows certain therapeutic interventions:
  - To remove an impacted food bolus or foreign body,
  - To dilate strictures with balloons or dilators,
  - To destroy a lesion by laser, cautery, or photodynamic therapy, and
  - To assist placing of implants or stents for advanced esophageal malignancy.

### Esophageal Manometry (Stationary and Ambulatory)

- Indicated to assess EMDs, especially if no obstructing lesion is identified by EGD or barium swallow. Esophageal peristaltic contractions—their amplitude, duration, velocity, and coordination, as well as upper and lower end sphincter pressure studies, and their temporal correlations between symptoms and reflux can be evaluated. On some patients esophageal manometry is used in combination with 24 hours pH monitoring to evaluate uncommon causes of dysphagia, e.g. DES, NE, achalasia, unexplained chest pain, and scleroderma.

### Esophageal 24-hours pH Reflux Study<sup>†† 6</sup>

- Accepted as the most accurate method for diagnosing reflux. It is, however, uncomfortable and expensive investigation. Therefore, indicated especially:
  - If barium swallow or EGD studies are negative,
  - In patients being considered for antireflux surgery, and

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<sup>††</sup> This technique has been revolutionized by a catheterless, wireless pH system.

- In the evaluation of patients with chest pain of undetermined origin.
- An abnormal result is indicated by a pH of <4 for more than 3% of the time when the patients are supine, and for >8% of the time when they are erect.

### **Videofluoroscopic Swallowing Function Study (VSFS)<sup>‡</sup>**

- The VSFS—performed jointly by a physician (typically a radiologist) and a speech-language pathologist—is the gold standard for evaluating the mechanism of swallowing. For this study, the patient is seated comfortably and given foods mixed with barium to make them radiopaque. The patient eats and drinks these foods while radiographic images are observed on a video monitor and recorded on videotape.
- VSFS permits close observation of all structures involved in swallowing process, i.e. lips, tongue, palate, pharynx, larynx, and proximal esophagus; indicated especially in patients at risk for silent aspiration, e.g. patients with stroke, or neurologic impairment such as cerebral palsy, MS, PD, MG, motor neuron disease, systemic sclerosis, and connective tissue disorders such as SLE, and RA.
- VSFS not only allows estimation of risks of aspiration and respiratory complications, but also helps in determining dietary modifications and training in swallowing techniques and maneuvers.

### **Radionuclide Study<sup>7</sup> (Tc-99m Sulfur Colloid Bolus)**

- These assess gastroesophageal reflux, esophageal motility disorders, or to identify silent aspiration. In GERD, reflux is present if the isotope is seen to travel back up into the esophagus. In esophageal motility disorders, computer programs measure

transit time in the upper, middle and lower thirds of the esophagus. Scintigraphy also can be combined with 24-hour pH manometry to check the cause of chest pain between esophageal and possible cardiac factors.

### **CT Scan/MRI**

- In suspected structural CNS abnormalities, e.g. primary or secondary tumors, MS; or, aortic vascular lesions, e.g. aneurysm, lusorian artery.

### **Muscle Enzymes**

- Elevated serum CK may be observed in motor neuron diseases, e.g. polymyositis, dermatomyositis.

### **TFTs**

- To detect hypothyroid or hyperthyroid disorders causing dysphagia, e.g. Graves' disease or thyroid carcinoma.

### **RF, ANA**

- In patients with autoimmune disorders, e.g. RA, SLE, scleroderma.

### **Antiacetylcholine Antibodies**

- Antiacetylcholine receptor antibody activity may be elevated in patients suspected with MG, and polymyositis.

### **Genetic Analysis**

- For example, in familial forms of ALS, or muscular dystrophy.

## **CLINICAL NOTES**

- It is important to ascertain that the patient truly has dysphagia, because some may misinterpret 'lump in the throat' (globus) as dysphagia
- The clinical features of 'globus' sensation may occur with organic disease in the neck, pharynx, or cervical esophagus; hence this diagnosis should only be made after a complete evaluation

<sup>‡</sup> The VSFS is similar to the MBS, except that the protocol for the MBS specifies quite small bolus volumes and does not include drinking from a cup. In practice, the terms "VSFS" and "MBS" are often used interchangeably.

- By asking following specific questions, the cause of dysphagia can usually be identified:
  - Do you have difficulty swallowing? In what way?
  - Do you have this sensation without swallowing food?
  - Can you localize dysphagia?
  - Do you have trouble with solids or liquids?
  - Is the swallowing difficulty greater for solids or liquids?
  - Is the dysphagia intermittent or progressive?
  - Do you have heartburn?
  - Any eating habits adopted to relieve symptoms?
  - Are there any associated problems, e.g. stress, cough, chest pain, dysphonia, collagen disease, immunosuppression, weight loss?
- Generally, dysphagia at the very beginning of swallowing characterizes oropharyngeal dysphagia; whereas dysphagia a few seconds after starting to swallow indicates an esophageal cause
- Onset—Acute dysphagia is commonly due to oropharyngeal causes such as infection, inflammation, food bolus impaction, or stroke (see above). Intermittent dysphagia suggests esophageal dysmotility syndrome, webs, or rings. Progressive dysphagia indicates an organic cause such as achalasia, carcinoma, mediastinal expanding lesion, or other systemic disorder, e.g. PD, scleroderma
- The type of bolus that elicits symptoms of dysphagia may indicate its cause (Table 15.2)
- *Odynophagia* often accompanies dysphagia in esophagitis, pharyngitis, opportunistic infections, pill esophagitis, diffuse esophageal spasm, rheumatoid arthritis (inflammation of cricoarytenoid joint), or malignant process involving the mucosa
- Associated signs and symptoms as important clues for possible cause of dysphagia are given in Table 15.3

**Table 15.2:** Types of bolus causing dysphagia

<i>Bolus</i>	<i>Cause of dysphagia</i>
Dysphagia with both liquids and solids from the outset	Muscular or neural control disorders of swallowing (bulbar, pseudobulbar palsy); motility disorders
Dysphagia initially for solids	Esophageal obstructive lesions (rings, webs, stricture)
Intermittent, non-progressive dysphagia, more for solids than liquids	Benign obstructive lesions (rings, webs, stricture); esophageal spasm
Progressive dysphagia first for solids, then for semisolids and liquids	Obstructive inflammatory stricture; achalasia; malignancy (carcinoma esophagus); scleroderma
Cold food or beverages precipitating dysphagia or causing chest pain	Esophageal dysmotility, especially spasm

**Table 15.3:** Signs and symptoms of causes for dysphagia

<i>Signs and symptoms</i>	<i>Diagnostic clues</i>
Sudden dysphagia	Obstructive dysphagia, esophagitis, brainstem stroke, acute thyroiditis, Rings and webs, DES, NE
Intermittent symptoms	Obstructive lesions, carcinoma, scleroderma
Progressive symptoms	Oropharyngeal dysphagia
Difficulty initiating swallow	Esophageal dysphagia
Food 'sticks' after swallow	Esophagitis—infection, pill-induced
Pain with dysphagia	Zenker's diverticulum
Regurgitation of old food, halitosis	
Ulcers on the tongue; tonsillar infection/abscess; retropharyngeal abscess	Lesions obvious on examination of the oral cavity
Tongue fasciculations	ALS
Pallor, koilonychia, hypochromic microcytic anemia	Plummer-Vinson syndrome
Mask-like facies, saliva drooling from the mouth, tremors, cog-wheel rigidity	Parkinson's disease
Drooping of eyelids, diplopia, swallowing becomes more difficult as meal progresses, extreme weakness	Myasthenia gravis
Palpable mass medial to sternomastoid	Pharyngeal pouch
Hoarseness of voice, visible neck, goiter, tracheal compression	Mediastinal syndrome, recurrent laryngeal nerve palsy, retrosternal goiter
Puckered and narrow mouth, inability to open mouth, thickened-hard-and-tight skin, Raynaud's Phenomenon	Scleroderma, progressive systemic sclerosis



- The *swallow test*<sup>§</sup>—The patient is observed during the act of swallowing liquids (a few ounces of water) and solids. Normally a person can drink/chew, mix, and propel a food bolus to the posterior pharynx without choking or coughing, and no significant amount of material is retained after a swallow. Drooling, delayed swallow initiation, coughing, throat clearing, or a change in voice may indicate a disorder. After the swallow, the patient is observed for a minute or more to see if there is delayed cough response indicating aspiration
- Oropharyngeal examination for ulcers, tonsillar infection, patch on mucosa, movements of the tongue, epiglottis, and soft-pallet, as well as examination of neck for masses, thyromegaly, and lymphadenopathy is important. Tongue fasciculations suggest ALS
- *Pharynx and Gag reflex*— Does the uvula elevate symmetrically when the patient says, “Aah”? Does the patient gag when the posterior pharynx is brushed? Unilateral movement of uvula or total absence of its upward movement, or gagging indicates palatal muscle paresis due to IX and X cranial nerve or brainstem lesion. Noting the patient’s speech and voice often confirm the oropharyngeal causes of dysphagia. The gag reflex needs to be tested only in patients with suspected brainstem pathology, impaired consciousness, or impaired swallowing
- A decreased gag reflex, though commonly associated with an increased risk of aspiration, absence of a gag reflex does not necessarily indicate that a patient is unable to swallow safely
- *Laryngoscopy*— Indirect laryngoscopy helps to confirm the diagnosis of lesions of oropharynx, larynx, and hypopharynx. Direct laryngoscopy may be indicated to evaluate obstructive or neuromuscular causes of oropharyngeal dysphagia. Changes in speech, hoarseness, or a weak cough may represent vocal cord paralysis. Slurred speech may indicate weakness or incoordination of

muscles involved in articulation and swallowing. Dysarthria, nasal speech, or regurgitation of food into the nose may represent weakness of the soft palate or pharyngeal constrictors. The combination of hoarseness, dysphonia (difficulty or pain in speaking), and nasal speech accompanying dysphagia is associated with the muscular dystrophies. Direct laryngoscopy also helps to differentiate dysphagia due to laryngopharyngeal reflux disorder (LPRD)<sup>§§</sup>, and GERD (Table 15.4). Laryngopharyngeal reflux (LPR) and GERD are different disorders. The term *LPR* is used to describe the acid in the stomach that comes up into the throat at the level of the laryngopharynx. LPR causes irritation and changes in the larynx. GERD is caused by the backflow of gastric contents into the esophagus, which leads to tissue damage or esophagitis and heartburn.

**Table 15.4:** Difference between GERD and LPRD

GERD	LPRD
<i>Symptoms</i>	
Mainly supine reflux	Mostly daytime, upright reflux
Heartburn and/or regurgitation common	Heartburn and/or regurgitation unusual
Hoarseness, cough, dysphagia, globus normally present	Hoarseness, cough, dysphagia, globus not usually present
<i>Physical findings</i>	
Laryngeal inflammation uncommon	Laryngeal inflammation common
Dysfunction of the lower Esophageal sphincter	Dysfunction of the upper esophageal sphincter
<i>Test results</i>	
Normal pharyngeal pH monitoring	Abnormal pharyngeal pH monitoring
Abnormal esophageal pH monitoring	Usually normal esophageal pH
Dysmotility	Good gastrointestinal motility
Erosive or Barrett’s Esophagus H uncommon	Erosive or Barrett’s esophagus may be present

<sup>§§</sup>LPRD is also termed as extraesophageal, reflux disorders, i.e. EERD.



- Neurologic examination includes testing of all cranial nerves, especially those involved in swallowing (sensory components of cranial nerves V, IX and X, and motor components of cranial nerves V, VII, X, XI and XII)
- Associated central nervous system deficits may suggest neuromuscular diagnosis, e.g. evidence of cogwheeling suggests Parkinson's disease; impaired memory indicates Alzheimer's disease or other dementia; ataxia, dementia or dysarthria suggests central nervous system disease.

### RED FLAGS

- Esophageal dysphagia, e.g. spasm, reflux esophagitis, may mimic angina pectoris in every respect, including site (retrosternal); radiation (neck, jaw, shoulder, thoracic spine, arm, epigastrium); nature (crushing or burning); vasovagal symptoms (pallor, sweating, tachycardia); and promptly relieved by nitroglycerine, or sublingual nifedipine, as in angina pectoris. The crucial historical differentiating points are—esophageal pain is generally much longer in duration (15-30 minutes), has no relation to exertion, and ECG or cardiac enzymes are normal
- In complicated cases, both esophageal and CAD may coexist; hence it is prudent to exclude CAD by more definitive tests such as barium esophagography, esophageal pH monitoring, Holter ECG monitoring, or stress thallium myocardial perfusion scintigraphy
- Consider esophageal disease as a possible cause in a patient with recurrent pneumonia; symptoms are often nocturnal due to tracheal aspiration or regurgitation of esophageal contents
- A new onset dysphagia may indicate esophageal cancer, especially in the elderly
- Dysphagia due to recurrent oral/pharyngeal ulcers or thrush may indicate an immunocompromised patient, especially with HIV infection
- Although patients with dysphagia usually present with a variety of signs and symptoms, these can be quite subtle or even absent, e.g. in those with silent aspiration.

### SELECTIVE GLOSSARY

**Amyotrophic lateral sclerosis (ALS)**—This is the most common variety of degenerative motor neuron disease, with a combination of UMN and LMN signs, although one type may predominate. Virtually all patients with ALS have dysphagia - the initial complaint is food sticking at the level of the cervical esophagus. Bulbar involvement leads to lip and tongue weakness, followed by jaw and suprahyoid weakness. This, in turn, leads to labial spillage, poor bolus propulsion, poor laryngeal elevation, depressed gag reflex, and poor airway protection. This disorder is sometimes associated with dementia or Parkinsonism.

**Barrett's esophagus**—BE is a condition in which columnar cells replace the usual squamous cell in the mucosa of the esophagus. The condition is recognized as a complication of GERD or inflammatory disorders of the esophagus. It occurs more often in men than in women (3:1 ratio); with the average age at diagnosis being 55 years. Barrett's esophagus does not produce symptoms distinct from GERD or esophageal inflammation. Most patients complain of heartburn pain, indigestion, blood in vomit or stool, difficulty in swallowing solid foods, or nocturnal regurgitation. Its importance lies in its predisposition to evolve into adenocarcinoma in the esophagus. EGD is the procedure of choice for the diagnosis of BE. The diagnosis requires biopsy confirmation (from 4 quadrants at standard intervals within the esophagus). Chromoendoscopy, i.e. vital staining with Lugol's solution performed at the time of upper

endoscopy to aid in cancer detection to identify abnormal mucosa, may be used as a means of esophageal cancer screening. In patients who are at increased risk for squamous cell carcinoma, the dye stains the glycogen in normal squamous epithelium a dark brown color. Areas that are unstained, particularly those that are larger than 5 mm in size, are likely to be dysplastic or malignant, and can be readily targeted for endoscopic biopsy.

**Dysphagia lusoria**—This is caused by a rare anomaly of the subclavian artery. This artery arises from the aortic arch distal of the left subclavian artery, crossing the midline, behind the esophagus. This abnormality is generally silent and often an incidental X-ray finding, but can result in dysphagia, which generally appears after the age of 40 years. The diagnosis can be overlooked at endoscopy, but barium contrast examination of the esophagus shows a characteristic diagonal impression at the level of the fourth thoracic vertebra. CT with contrast study or MR angiography confirm the diagnosis and exclude aneurysms.

**Eosinophilic esophagitis**—This is an emerging cause of dysphagia, typically seen in young adults. Often, the history of dysphagia dates to adolescence. In children it is responsible for feeding disorders, vomiting, reflux symptoms and abdominal pain, and in adults it causes intermittent solid food dysphagia or food impaction. The natural history of this disorder has not been well-characterized, but appears to be marked by periods of spontaneous remission and exacerbations that are not linked to specific factors, although food allergies and exposure have been implicated. Some have a history of atopy. Endoscopy may reveal a number of subtle features that include a 'corrugated' esophagus with fine rings; a diffusely narrowed esophagus that may have proximal strictures; the presence of linear

furrows, adherent white plaques, or a friable (crepe paper) mucosa, prone to tearing with minimal contact; or even normal looking esophagus. Frank esophagitis is not part of the macroscopic endoscopic picture of eosinophilic esophagitis. The most important element in the diagnosis of eosinophilic esophagitis is to know its macro- and micromorphological characteristics. Biopsies from the proximal to the distal esophagus demonstrating > 15-20 eosinophilic granulocytes per high powered field favor the diagnosis. With increasing recognition, this entity is taking its place as an established cause of solid food dysphagia.

**Progressive systemic sclerosis**—Patients with progressive systemic sclerosis usually present with heartburn, dysphagia, and regurgitation. The oral, pharyngeal, and esophageal phases of swallowing can all be affected. Progressive atrophy and fibrosis of esophageal smooth muscle is usually prominent. Gastroesophageal reflux is frequent. Esophageal manometry typically shows lower pressures and sometimes aperistalsis. Poor peristalsis, decreased lower esophageal sphincter pressures, and gastroesophageal reflux can result in a transition from a patulous dilated esophagus to one that is strictured and scarred. Barrett esophagus may develop. The presence of oropharyngeal disease is usually accompanied by pulmonary disease. Patients with progressive systemic sclerosis may also have xerostomia (which is frequently due to medications), dental problems (due to fibrosis of the ligamentous tooth attachments), trigeminal nerve involvement (decreased bolus sensation), and lingual atrophy that can also contribute to dysphagia.

**Schwartz ring** (*pronounced - shats-ke or schatz-ki's ring*)—This is narrowing in the lower part of the esophagus, consisting of a membrane-like structure, lined by squamous epithelium on its superior aspect and columnar epithelium inferiorly. Such a ring is quite common, being

detected in up to 10% of all upper GI barium X-rays. Few produce sufficient luminal obstruction to cause dysphagia. When the lumen is narrowed to a diameter of 13 mm or less, the patient will experience intermittent solid-food dysphagia or even episodic food-bolus obstruction.

**Sjögren's syndrome** (*pronounced* — “SHOW-grins”) — SS is a chronic disease, probably due to auto-immunologic factors with genetic predisposition. Viral infections such as Epstein-Barr virus (EBV), human T-lymphotrophic virus 1 (HTLV-1), human herpesvirus 6 (HHV-6), human immunodeficiency virus 1 (HIV-1), hepatitis C virus (HCV), and cytomegalovirus (CMV) could be involved in the induction of SS. Women are affected more often than men — the female-to-male ratio is 9:1; usually occurring between 30-50 years. The hallmark symptoms are the “sicca complex”, a combination of dry eyes (keratoconjunctivitis sicca—KCS) and dry mouth (xerostomia). SS can affect the oral phase of swallowing when the salivary glands are involved. The oral dryness of SS leads to difficulty swallowing dry food, unless they are washed down with liquids. Patients with xerostomia have a delayed swallow; some patients will have dysphagia for solids and some may take longer to complete a meal. Abnormal esophageal motility consists of absent or decreased contractility in the upper third of the esophagus, while decreased esophageal peristalsis can be seen in the distal esophagus. SS occurs in a *primary* (glandular) form not associated with other diseases (i.e. KCS and xerostomia only) and in a *secondary* (extraglandular) form (i.e. KCS, xerostomia, and an autoimmune disease). Most commonly, this autoimmune disease is RA. The disease is usually benign; however, in a few with systemic involvement, there is increased incidence of non-Hodgkin's lymphoma.

**Wallenberg or lateral medullary or posterior inferior cerebellar artery (PICA) syndrome** — It is a type of brainstem (medulla and cerebellum)

stroke manifested by imbalance, vertigo, difficulty swallowing, hoarseness of voice, and sensory disturbance. Brainstem stroke is associated with a higher frequency of dysphagia. This is because the swallowing response control center resides primarily in the medulla. These patients often exhibit dysphagia at 1–2 weeks after stroke, but can make improvements up to week 3. Common problems include delayed or absent swallow response, unilateral pharyngeal paresis, and upper esophageal sphincter dysfunction. VSFS demonstrates a lack of upper esophageal sphincter (UES) opening during swallow in patients with lateral medullary syndrome, leading to varying degrees of aspiration.

**Zenker's diverticulum** — It is also called a *pharyngo-esophageal diverticulum* — an outpouching of posterior hypopharyngeal wall at an area of potential weakness in the inferior pharyngeal constrictor muscle referred to as the Killian dehiscence (usually at the C5/6 level), seen most commonly in the elderly, in the seventh or eighth decade of life. The most common presenting feature is upper esophageal dysphagia; other common symptoms include halitosis, regurgitation of undigested food, noisy swallowing, and aspiration. Hoarseness can be present when the diverticulum is large enough to compress the recurrent laryngeal nerve. Some patients also report excessive salivation and the sensation of a mass within the throat. A very large diverticulum can produce an external neck mass, usually on the left side. Weight loss and recurrent pulmonary infections occur in approximately one-third of patients. There is an association with hiatal hernia, gastroduodenal ulcer, midesophageal diverticulum, esophageal spasm, and achalasia. Fluoroscopic barium esophagography is the mainstay of diagnosis of Zenker diverticulum. Care must be taken in performing endoscopy in patients with known Zenker diverticulum, as passage of the endoscope into the diverticulum carries some risk of perforation.

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## CHAPTER

# 16

## Dyspnea—Acute

### SYNOPSIS

Literally the term *dyspnea* means difficult breathing. Clinically, dyspnea is a term applied to sensations experienced by individuals who complain of unpleasant or uncomfortable respiratory sensations. The sensation of dyspnea is subjective\*, and includes both the perception of labored breathing by the patient and the reaction to that sensation,<sup>1,2</sup> which varies in quality and intensity. A recent consensus statement from the American Thoracic Society offered the following definition of dyspnea: “Dyspnea is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses.”<sup>3</sup>

A person with dyspnea may describe this symptom in terms such as shortness of breath, breathlessness, choking sensation, or tightness in the chest. Subjectively (i.e. from the patient’s

point of view), patient with acute dyspnea experiences abnormally uncomfortable awareness of breathing, which is accompanied by objective findings such as tachypnea, increased respiratory effort, distress, and even altered mental status. The patient in such an attack of acute dyspnea is classified as belonging to class III or class IV gradation based on New York Heart Association classification; i.e. dyspnea on minimal exertion or dyspnea at rest respectively.

Acute dyspnea<sup>†</sup> is a cardinal symptom affecting the cardiopulmonary system, and can be a sign of potentially fatal illness (e.g. MI and pulmonary embolism); hence all reasonable methods should be used to distinguish between cardiac and pulmonary causes of dyspnea as rapidly as possible, so as to improve outcomes and patient survival.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Status asthmaticus
- Acute exacerbation of COPD

\*Like pain, dyspnea is a sensory experience that is perceived, interpreted, and rated solely by the patient himself.

<sup>†</sup>Acute dyspnea may be considered as ‘sudden’, i.e. within seconds to minutes, and ‘acute’, i.e. within hours to days.

- Pneumonia (especially in immunocompromised or immunodeficiency patients such as HIV disease and alcoholics)
- Acute laryngotracheobronchitis (Croup)
- Acute LVF (due to MI, pericarditis, cardiac tamponade, fulminant myocarditis)
- Arrhythmias (VT, AF, VF)
- Psychogenic (hyperventilation syndrome).

#### Occasional

- Spontaneous or tension pneumothorax
- Massive pleural effusion (tubercular, malignant)
- Massive lobar collapse (traumatic, post-operative)
- Massive pulmonary embolism (PE)
- Metabolic acidosis (DKA, uremia, salicylate overdose)
- Anaphylaxis (angioneurotic edema)
- Severe acute respiratory syndrome (SARS).

#### Rare

- Foreign body aspiration
- Drug induced (NSAIDs, beta blockers)
- Acute respiratory distress syndrome (ARDS)
- Neurologic (CVA, Guillain-Barré syndrome, Bulbar polio)
- Pacemaker syndrome.

### INVESTIGATIONS—GENERAL

#### CBC

- Anemia aggravates dyspnea of any etiology
- WBC count may be increased in pulmonary infection
- Significant eosinophilia is commonly reported in asthma
- Thrombocytopenia may accompany ARDS.

#### Blood Glucose, Electrolytes, Urinalysis

- To exclude hyperglycemia, and DKA
- Renal and electrolyte abnormalities can precipitate acute dyspnea.

#### Peak Expiratory Flow Rate (PEFR)

- Reduced flow rate of < 150 l/mit (normal value 400-600 l/mit) indicates obstructive pulmonary disease that may require hospitalization; its complete reversibility is diagnostic of asthma.

#### ECG

- Although in most dyspneic patients the ECG does not contribute much to diagnosis, it does indicate whether heart disease of any disorder is present, such as cardiac ischemia, arrhythmia, chamber hypertrophy, and heart block. These cardiac disorders can contribute to acute dyspnea. Also, lung disease eventually affects right side of the heart, and may cause changes suggesting lung disease such as right atrial or right ventricular hypertrophy in pulmonary hypertension
- The complex of an S wave in lead I, a Q wave in III, and an inverted T wave in lead III is specific for pulmonary embolism, but rarely seen.

#### CXR

- Can demonstrate consolidation, infiltrate, effusion, pneumothorax, bullae, pulmonary edema, tumor, and cardiomegaly
- In pulmonary embolism, the CXR is usually normal, but abnormalities include focal oligemia (i.e. Westermark's sign); a peripheral wedge shaped density (i.e. Hampton's hump); pleural effusions; elevated hemidiaphragm; or an enlarged right descending pulmonary artery (i.e. Palla's sign).

#### X-ray Neck — Lateral View

- May be indicated in patients with stridor, e.g. to exclude obstructive lesion or foreign body aspiration.

#### Pulse Oximetry

- Used as a rapid method for assessment of oxygenation; hypoxemia of <90% on pulse



oximetry indicates further ABG estimation for precise evaluation of dyspnea.

### **Sr Cardiac Markers**

- Cardiac troponin and CK-MB is elevated with MI in the setting of acute LVF.

## **INVESTIGATIONS—SPECIFIC**

### **Sputum and Blood Culture**

- They are of value when infective etiology such as pneumonia, lung abscess is suspected. In an acutely dyspneic patient the value of sputum examination depends on the production of uncontaminated sputum sample.

### **Pulmonary Function Tests**

- Spirometry—With increasing airflow limitation,  $FEV_1$  falls proportionately more than the FVC, so that the  $FEV_1/FVC$  ratio is reduced.

### **Arterial Blood Gases (ABG)**

- Useful in assessing the type, degree of respiratory failure, and measuring the overall acid-base status
- An increased pH with decreased  $pCO_2$  indicates acute respiratory alkalosis, whereas both decreased pH and bicarbonates indicate metabolic acidosis, such as due to DKA. However, normal levels of oxygenation are not useful to exclude respiratory or cardiac diseases causing acute dyspnea.

### **Bronchoscopy**

- It should be performed if aspiration of foreign body is suspected; the procedure can be both diagnostic and therapeutic.
- It also allows collection of bronchial secretions for bacteriological/cytological examination.

### **D-dimer**

- This is useful in determining risk for DVT or PE.

### **HRCT of Thorax**

- Spiral CT scanning of the chest with iodinated contrast is gradually replacing ventilation-perfusion lung scanning as the screening procedure of choice for the diagnosis of pulmonary embolic disease
- V/Q scans are recommended only if spiral CT is not available
- MR angiograms are recommended as a first line investigation only if spiral CT is contraindicated.

### **V/Q scan**

- V/Q scan should be used in cases where results of HRCT are inconclusive, which may necessitate the use of pulmonary angiography.

### **BNP (Brain or B-type Natriuretic Peptide)**

- This test is useful to evaluate for the presence of CHF in patients with dyspnea. A low value ( $<80$  pg/ml) has a high (99%) negative predictive value that helps to rule out CHF; a high value ( $>100$  pg/ml) is nonspecific, but is about 90% sensitive for CHF.

### **Echocardiography**

- This procedure is indicated if CHF, valvular heart disease, or pericardial effusion is suspected. It also helps to identify an embolus in suspected PE. Pulmonary artery pressure can also be estimated to rule out pulmonary hypertension causing dyspnea.

### **Drug Screen**

- Serum levels of salicylates and other drugs (e.g. Amiodarone) suspected to be responsible.

## CLINICAL NOTES

- In an acutely dyspneic patient it is important to ensure that the Airway, Breathing, Circulation (ABC) are attended to before continuing with the diagnostic process. Life-threatening problems must be excluded during initial examination (Table 16.1). The following checklist of questions is useful in practice:

**Table 16.1:** Life-threatening causes of dyspnea

- Myocardial infarction
- Ventricular tachycardia
- Status asthmaticus
- Pulmonary embolism
- Tension pneumothorax
- Anaphylactic laryngeal edema
- Airway obstruction
- Diabetic ketoacidosis
- Guillain-Barré syndrome
- Carbon monoxide poisoning
- Salicylate poisoning

- Is it dyspnea or a condition stimulating it?
- Is it due to cardiac dysfunction?
- Is it due to pulmonary dysfunction?
- If cardiac, what is the grade of dyspnea?
- Is there PND or orthopnea?
- Is the patient receiving drugs; if so what is the response?
- What are the associated symptoms?
- Once an emergent situation has been excluded, reassess the patient's airways, mental status, ability to speak, and breathing effort, and question the patient (or a family member) about duration of the dyspnea, any underlying cardiac or pulmonary disease, medication use, cough, fever, chest pain, and trauma
- Dyspnea should be differentiated from tachypnea and hyperventilation which refer to respiratory variations regardless of the patient's subjective sensations. *Tachypnea* is

the objective finding of a rapid respiratory rate and may or may not be associated with the feeling of not being able to breathe properly; tachypnea may be necessary for a sufficient gas-exchange of the body, for example after exercise, in which case it is not hyperventilation. *Hyperventilation* (or overbreathing) is an increase in the respiratory rate above normal — a state of breathing faster and/or deeper than necessary, thereby reducing the carbon dioxide concentration of the blood below normal. These conditions may not always be associated with dyspnea. *Orthopnea* is the sensation of breathlessness in the recumbent position, relieved by sitting or standing. Two uncommon types of breathlessness are *trepopnea* and *platypnea*. *Trepopnea* is dyspnea that occurs in one lateral decubitus position as opposed to the other (e.g. in patients with unilateral lobectomy, pneumonectomy). *Platypnea* refers to breathlessness that occurs in the upright position and is relieved with recumbency (e.g. hepatopulmonary syndrome, cardiac shunt — Tetralogies of Fallot)

- Although the diagnosis of hyperventilation syndrome is suggested by associated symptoms of panic and anxiety, or frequent sighing, it is wise to exclude cardiopulmonary diagnosis before arriving at this diagnosis
- Differentiation between bronchial asthma and cardiac asthma is critical (Table 16.2). However, both cardiac and pulmonary disease and/or disorders of different systems may coexist in the same patient; e.g. LVF and COPD, pneumonitis and ARDS, respiratory muscle paralysis and aspiration pneumonia

**Table 16.2:** Clinical differentiation between cardiac and bronchial asthma

Points	Cardiac asthma	Bronchial asthma
Age	Usually elderly or older	Any age
Past history	CAD, hypertension, valvular disease	Previous attacks of asthma, atopy
Family history	Usually non-contributing	Generally positive
Precipitating factors	Exertion, infraction	Exposure to allergens
Symptoms	Cough, frothy expectoration prominent; wheezing not marked	Cough, thick stick sputum; wheezing marked
Pulse	Rapid; pulses alternans may be present	Rapid; may be feeble in severe/prolonged asthma; no pulses alternans
Auscultation	Triple rhythm, murmurs, pericardial rub	Normal heart sounds
Breath sounds	Expiration not prolonged, basal crepts prominent	Expiration markedly prolonged; wheezing all over chest

- Intensity of wheezing is unreliable. Some patients with asthma do not wheeze and some who wheeze do not have asthma
- The presence of orthopnea or paroxysmal nocturnal dyspnea (PND) is more suggestive of cardiac failure than of lung disease
- Deep 'sighing' respiration (Kussmaul respiration, air hunger) of acidosis, usually seen in diabetic and uremic patients, or Cheyne-Stokes respiration (periodic breathing), usually seen in cerebrovascular disease, or poisoning, should not be mistaken for acute dyspnea
- Subcutaneous emphysema should raise suspicion of associated pneumothorax.
- A review of medications may provide useful clues to the possible cause of the dyspnea,

especially in the evaluation of a new patient. For example, use of an inhaler would point to a possible history of asthma or COPD. If patient is taking furosemide he may have a history of CHF

- Angioedema, characterized by facial, extremity, and airway edema, may cause difficulty breathing, and is a possible adverse effect seen in patients who begin taking an ACE inhibitor such as captopril
- Cardiac tamponade related to trauma or HIV is more common in young adults, whereas tamponade due to malignancy and/or renal failure occurs more frequently in elderly individuals
- A diagnostic strategy that combines a high degree of *clinical suspicion*; careful evaluation of *historical and clinical findings* (e.g. dyspnea, pleuritic chest pain, tachypnea, and tachycardia); *risk factors* for venous thromboembolism (e.g. recent surgery or immobilization, stroke, CHF, cancer, fracture of the pelvis, femur or tibia, obesity, pregnancy or recent delivery; estrogen therapy; inflammatory bowel disease, and various genetic or acquired thrombophilia); and corroborative findings from noninvasive diagnostic techniques (e.g. D-dimer, HTCT of lungs) can improve diagnostic accuracy of PE. However, many cases of PE are indeed clinically silent
- Physical examination— Common physical findings are listed in Table 16.3.

## RED FLAGS

- Respiratory rate over 30/mit, pulse rate over 120/mit, and pulsus paradoxus greater than 18 mm Hg indicate a dangerously severe episode of dyspnea
- Dyspnea at rest, orthopnea, sweating, and difficulty speaking in sentences, use of accessory muscles of respiration, decreased

**Table 16.3:** Physical examination findings in the diagnosis of acute dyspnea in adults and children

Findings	Possible diagnosis
Cyanosis, wheezing, pulsus paradoxus, accessory muscle use	Acute asthma, COPD exacerbation
Wheezing, clubbing, barrel chest, decreased breath sounds	COPD exacerbation
Fever, localized crepts, increased fremitus	Pneumonia
Edema, JVP, S <sub>3</sub> or S <sub>4</sub> gallop rhythm, hepatjugular reflux, murmurs, basal crepts, hypertension	CHF, LVF
Beck triad-distended JVP, hypotension, muffled heart sounds	Cardiac tamponade
Pulsus paradoxus, pericardial rub	Cardiac tamponade, severe asthma
Chest pain, localized crepts, friction rub, edema feet, calf swelling, recent child delivery	DVT, pulmonary embolism
Absent breath sounds, hyper resonance	Pneumothorax
Trauma, surgery, shock	ARDS
Inspiratory stridor, rhonchi, retractions	Acute laryngo-tracheobronchitis (Croup)
Stridor, drooling, fever	Epiglottitis
Stridor, wheezing, persistent pneumonia	Foreign body aspiration
Wheezing, flaring, intercostal retractions, apnea	Bronchiolitis
Sighing	Acidosis, hyperventilation

mental status or consciousness indicate a life-threatening situation and constitute an indication for urgent intubation

- In a case of asthma, absence of wheezing (silent chest) or decreased wheezing can indicate worsening obstruction
- No single noninvasive test or clinical evaluation can definitively point to a diagnosis of PE, and this frequently missed diagnosis may have fatal consequences
- Cardiac tamponade is a medical emergency. Early diagnosis and treatment are crucial to reduce morbidity and mortality. Untreated, it is rapidly and universally fatal.

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## CHAPTER

# 17

## Dyspnea—Chronic

### SYNOPSIS

Breathlessness that persists for more than a month may be termed as chronic dyspnea. This symptom is present in many different illnesses. Fortunately, only a few disorders are seen in practice; therefore, a logical and time saving first step is to do a rapid assessment of the patient's general level of distress and vital signs to exclude the causes for acute dyspnea.\* The next step is to evaluate the patient for the possible causes of chronic dyspnea.

A patient with chronic dyspnea may present with any of the following four grades based on New York Heart Association classification:

- Class I – Disease present but no dyspnea or dyspnea only on heavy exertion
- Class II – Dyspnea on moderate exertion
- Class III – Dyspnea on minimal exertion
- Class IV – Dyspnea at rest.

It is more useful, however, to determine the amount of exertion that actually causes dyspnea, i.e. the distance walked, or the number of steps climbed to assess the functional

capacity. Although there are many tests or protocols developed to assess individual's functional capacity, they are prone for subjective errors by either overestimating or underestimating their true functional capacity. Therefore the American Thoracic Society (ATS) has issued standardized guidelines for the *6-minute walk test* (6MWT: *vide infra* ↓↓), which is safe, easier to administer, better tolerated, and better reflects functional cardiopulmonary status and activities of daily living.<sup>1-5</sup>

### DIFFERENTIAL DIAGNOSIS

#### Common

- Asthma
- COPD (chronic bronchitis, emphysema)
- CHF
- IHD (angina: stable, unstable)
- Postnasal drip syndrome
- GERD
- Morbid obesity (rapid weight gain)
- Sedentary lifestyle (physical deconditioning)
- Psychogenic (GAD, PTSD, panic disorder).

\* Ref: Chapter 16: Dyspnea—Acute.

**Occasional**

- Anemia (chronic)
- Bronchiectasis
- Pleural effusion (bacterial, malignant)
- Interstitial lung diseases (i.e. ILD, sarcoidosis, pneumoconiosis)
- Valvular heart diseases (mitral stenosis, aortic stenosis, ASD, VSD)
- Cardiac arrhythmias (AF)
- Recurrent pulmonary embolism
- Upper airway obstruction (foreign body, tonsillar obstruction, vocal cord paralysis, external compression, tracheal tumors)
- Lung cancer (primary, metastatic).

**Rare**

- Pulmonary hypertension (usually secondary to COPD, ILD)
- Intracardiac shunts
- Cardiomyopathies
- Pericardial disease
- Severe kyphoscoliosis
- Drug induced (cytotoxic agents, amiodarone, nitrofurantoin, gold)
- Neuromuscular diseases (Guillain-Barré syndrome, myasthenia gravis, amyotrophic lateral sclerosis, i.e. ALS).

**INVESTIGATIONS—GENERAL****CBC**

- Low Hb% and hematocrit values are features of anemia
- Leukocytosis may be seen in superadded pulmonary infection
- Erythrocytosis may be seen with any chronic pulmonary or cardiac cause of chronic dyspnea
- Eosinophilia may be seen in chronic asthma.

**Sputum**

- Gram stain for pneumococcal pneumonia; ZN stain for mycobacteria; and Giemsa's

stain for *Pneumocystis carinii* pneumonia may be useful.

**CXR**

- This can demonstrate effusion, pneumothorax, and cardiomegaly, signs of CHF, fibrosis, tumor, or hilar lymphadenopathy
- In ILDs it may demonstrate a linear fibronodular, or fibroreticular infiltrate
- In COPD such as chronic bronchitis and emphysema, signs of hyperinflation of the lungs, tapering vascular shadows, and bullous changes may be seen.

**Pulse Oximetry**

- Useful method for rapid assessment of oxygenation. In severe COPD, ILDs, desaturation at rest with values of  $S_{PO_2}$  less than 90% is a sensitive indicator of gas exchange abnormalities. If abnormal, consideration should be given to obtaining arterial blood gas measurements.

**ECG**

- In almost all forms of chronic pulmonary disease, ECG may show right axis deviation, right ventricular enlargement and strain, right atrial enlargement, atrial arrhythmias. RBBB may occur in long-standing lung disease. Evidence of left ventricular disease (ischemia, hypertrophy), pericardial disease may be seen in chronic left sided heart failure
- Sinus tachycardia is frequent in severe anemia and thyrotoxicosis.

**Metabolic Panel**

- Changes in acid-base balance reflected by the bicarbonate level in a metabolic panel may provide a clue to dyspnea. In severe chronic lung diseases such as COPD, asthma, ILDs, neuromuscular disorders with hypoventilation, the serum bicarbonate level may be increased
- Dilution hyponatremia may be seen in CHF.



### Blood Chemistry

- Sr creatinine, and urea will often be found to be high in patients with severe anemia; and presence of albuminuria, especially when associated with hypertension
- Sr calcium value may be elevated in sarcoidosis.

## INVESTIGATIONS—SPECIFIC

### PFT/Spirometry

- Formal spirometry differentiates restrictive and obstructive lung disorders<sup>†</sup> (Table 17.1). It can also provide information regarding severity of the disease and response to inhaled bronchodilators. Other measurements and lung volumes, and diffusion capacities such as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), total lung capacity (TLC), residual volume (RV), and diffusion capacity of lung for carbon monoxide (DLCO) are useful in differentiating various pulmonary and cardiac causes of dyspnea. However, results of spirometry need to be evaluated in relation to reference values.<sup>6,7</sup>

### Methacholine Challenge Test

- This test is used if the symptoms of dyspnea are intermittent, or lung disease is suspected and PFTs are normal.

### Echocardiography

- Indicated in patients with cardiac causes of chronic dyspnea, especially if heart failure is suspected. Other indications include cardiac valvular dysfunction, pulmonary hypertension, and pericardial disease.

**Table 17.1:** Diseases commonly associated with restrictive and obstructive lung diseases

<i>Restrictive breathing pattern</i>	<i>Obstruction to airflow</i>
Intrinsic lung disease	Lower airway obstruction
Pneumonia	Asthma
CHF	Chronic bronchitis
Pleural effusion and pleural disease	COPD
Advanced malignancy	Emphysema
Lung fibrosis	Cystic fibrosis
Sarcoidosis	
Acute respiratory failure with pulmonary edema	External compression of bronchus
Hyaline membrane disease	Lymph nodes, mediastinal mass, vascular aneurysm
Collagen vascular disease	
Drugs: chemotherapeutics	
Occupational toxic exposure	Upper airway obstruction
Lung transplant	Laryngotracheobronchitis
CNS causes	Epiglottitis
Guillain-Barré syndrome	Foreign body
Myasthenia gravis	Bronchial stricture
Poliomyelitis	
Diaphragm paralysis	Others
Others	Alpha-1 antitrypsin deficiency
Morbid obesity	Kartagener's syndrome
Flail chest	Bronchomalacia
Spinal deformity	

### B-type Natriuretic Peptide (BNP)

- Plasma BNP, a neurohormone, its major source is cardiac ventricles, suggesting that BNP may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides. It is released in response to pressure/volume overload, resulting in increased wall tension. The magnitude of elevation is proportional to the severity of heart failure. BNP test may be helpful, especially in patients who have coexisting cardiac and pulmonary disease, and are found to be very reliable in differentiating CHF from pulmonary disease.<sup>8-10</sup>

### HRCT

- HRCT is especially helpful in diagnosing unsuspected ILD. It is the preferred test for diagnosing bronchiectasis, and can identify both acute and chronic PE, particularly in larger vessels.

<sup>†</sup> The two breathing patterns frequently are seen together in one disease.

**HRCT Angiography**

- Conventional pulmonary angiography is currently replaced by HRCT angiography, which has better sensitivity and specificity in patients presenting with isolated or chronic dyspnea.<sup>11,12</sup>

**V/Q Scan**

- Unlike in acute massive PE wherein V/Q scan usually shows major areas of decreased perfusion diagnostic of PE, this investigation in chronic PE may show no abnormality. Most V/Q scans revert to normal after 24 hours of the episode.

**24-hour Esophageal pH Monitoring**

- GERD may be clinically silent, except for the symptoms of dyspnea and may require ambulatory esophageal monitoring to confirm the diagnosis. Studies have identified an association between gastroesophageal reflux and chronic dyspnea despite normal pulmonary function tests. Reflux may stimulate vagal reflexes that inhibit diaphragmatic function, thereby causing breathlessness. This etiology can be established by performing a 24-hour pH monitoring.

**EMG and NCS**

- These tests are useful for confirming and differentiating neuromuscular disease such as Guillain-Barré syndrome and myasthenia gravis.

**Noninvasive Cardiovascular Testing**

- In some patients with coronary artery disease, dyspnea may represent an anginal equivalent. Noninvasive cardiovascular testing (e.g. stress thallium, stress echocardiography, cardiac magnetic resonance imaging) and/or cardiac catheterization should be considered for these patients.

**Cardiopulmonary Exercise Testing (CPEx)**

- This procedure helps quantify cardiac function, pulmonary gas exchange, ventilation, and physical fitness. It is especially useful in cases where no apparent cause for dyspnea is found after a thorough evaluation or in patients who have multiple potential causes for dyspnea. Parameters that are measured by computerized systems are blood pressure, electrocardiography, heart rate, ventilation, oxygen saturation, oxygen uptake, and carbon dioxide output. In normal individuals, pulmonary capacity is greater than cardiac. By determining the function of both the cardiac and pulmonary systems, the relative degree of impairment can be used to guide therapy.

**Bronchoscopy / Lung Biopsy**

- Lung biopsy may be indicated in cases of ILD that are difficult to diagnose or when malignancy is suspected.

**CLINICAL NOTES**

- The first step in the evaluation of patients with chronic dyspnea is to establish the primary organ/system involved – pulmonary, cardiac, both, or neither
- Specific questions regarding change in weight, exercise habits, occupational exposures, asthmatic triggers, cardiac risk factors (diabetes, hyperlipidemia, hypertension, and tobacco abuse) psychiatric history, sources of stress and anxiety, or symptoms of GERD should be asked
- History of connective tissue disorders such as rheumatoid arthritis, polymyositis, and scleroderma is suggestive of ILDs causing chronic dyspnea
- History of endotracheal intubation, tracheostomy is suggestive of upper airway obstruction causing dyspnea

- In a patient with history of chronic, episodic dyspnea with superficial/hilar lymphadenopathy, arthralgia, cutaneous nodules, and raised serum calcium is suggestive of sarcoidosis
- Progressive dyspnea may be the initial manifestation of carcinoma of lung, breast, stomach, prostate, or other organs
- Common physical findings are listed in Table 17.2.

**Table 17.2:** Clinical findings and causes of chronic dyspnea

Clinical findings	Cause
Intermittent breathlessness; prolonged expiration; wheezing; atopy; triggering factors	Asthma
Tobacco abuse; barrel chest; prolonged expiration; wheezing	COPD
Orthopnea; PND; JVP; pedal edema; S <sub>3</sub> ; basilar crepts; hypertension; CAD;DM	CHF
Panic disorder; GAD; PTSD;	Psychogenic
Postprandial dyspnea	GORD
Decreased or absent breath sounds Hemoptysis	Pleural effusion; Pneumothorax Lung malignancy; pneumonia; Bronchiectasis; mitral stenosis; Arteriovenous malformation
Recurrent pneumonia	Lung malignancy; bronchiectasis; Foreign body
Accentuated P2; right ventricular heave; Murmur	Pulmonary hypertension
Exposure to organic dust	Pneumoconiosis
History of immunosuppressive disease or therapy; AIDS	<i>P. carinii pneumonia</i> ; TB; fungal
History of intubation; tracheostomy Drug exposure	Upper airway obstructive disease B-Blockers causing bronchospasm; Amiodarone / nitrofurantoin causing pneumonitis; methotrexate causing lung fibrosis

## RED FLAGS

- Dyspnea in older people may be associated with disease in a single or more likely multiple organs
- The common causes of dyspnea are frequently over diagnosed when a less common cause of dyspnea is actually present; e.g. dyspnea in an elderly smoker is commonly diagnosed as bronchitis (smoker's cough), which could have been due to lung carcinoma

- Chronic cough/dyspnea are commonly treated as 'allergic', which could have been due to ILDs
- Chronic dyspnea may present as an acute event; e.g. acute LVF in CHF; pneumothorax in chronic asthmatic; pulmonary embolism in valvular heart disease
- ILDs may present with minimal physical signs or CXR findings, especially in early stages, despite the presence of significant dyspnea
- The presence of COPD doubles the risk of lung cancer in smokers, independent of their smoking history.<sup>13,14</sup>

## SELECTIVE GLOSSARY

**Six-minute walk test (6MWT)**—The ability to walk for a distance is an easy way to measure exercise capacity in patients with cardiac and pulmonary diseases. A variety of walk tests, including self-paced walk tests, controlled-pacing incremental walk tests, and time-paced tests are considered to be objective measurements of functional capacity. The 6MWT is an objective, submaximal exercise test method, used as a clinical indicator of the functional capacity in patients with moderately severe impaired cardiopulmonary diseases such as COPD, ILD, pulmonary hypertension, heart failure, and peripheral arterial diseases, and ability to perform daily living activities. It is also performed to monitor therapy, or assess the prognosis in patients with cardiac and pulmonary diseases. With 6MWT the instructions to the patient are to "walk as far as you can during 6-minutes" on a level and straight track; and not an oval or circular track. The new ATS guidelines provide a standardized approach for performing the test. In comparison to traditional pulmonary exercise test, 6MWT needs less technical support or equipment, making it a simple and inexpensive method to

measure functional capacity. The six minute walk distance (6MWD) can be correlated with patient's height, BMI, Borg scale, spirometric parameters and diffusion capacity. Absolute contraindications to the test include an history of unstable angina or MI during the previous month; relative contraindications include resting tachycardia (heart rate >120/mit), uncontrolled hypertension, or arthritis and other musculoskeletal disease.

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## CHAPTER

# 18

## Facial Asymmetry and Weakness

### SYNOPSIS

Careful studies have shown that mild to moderate facial asymmetry is, in fact, the norm. On average, both men and women have right hemi-face dominance. This normal asymmetry is usually not prominent on visual scrutiny. Facial asymmetry is said to exist only when the asymmetry exceeds the balance that we accept as normal.<sup>1,2</sup>

Symmetry of the face (i.e. facial configuration in general) depends primarily on the functional integrity of its muscles, and the movement of these facial muscles of each side is controlled by the seventh cranial nerve (CN VII).<sup>\*</sup> If both (i.e. right and left) facial tracts are intact from the cortex (center) to the periphery, the muscles will move symmetrically. Hence, any lesion in the course of its central and/or peripheral pathway mainly manifests as weakness or asymmetry of facial muscles.<sup>†</sup>

<sup>\*</sup> Most of the present discussion about facial asymmetry is related to acquired disorders of CN VII palsy. For facial asymmetry *not* due to facial nerve palsy, refer to Page no. 125, Table 18.5: Differential diagnosis of altered facial counter.

<sup>†</sup> Taste sensation in the anterior part of the tongue may also be affected.

From therapeutic and prognostic point of view, it is critical to differentiate this peripheral (i.e. nuclear) nerve palsy from the central (i.e. supranuclear) lesions of the CN VII; the latter manifests only in the lower divisions of the seventh nerve because of the bilateral cortical representation. Thus, a central CN VII (upper motor neuron, i.e. UMN) lesion involves only the lower face (i.e. upper half escapes), while the usually benign and self-limited peripheral (lower motor neuron, i.e. LMN) lesion affects the entire half of the face on the affected side. Besides the UMN and the LMN facial nerve palsy, facial weakness and asymmetry is also seen in muscle or neuromuscular junction disorders.

Patient with obvious facial asymmetry or weakness, besides disfigurement, suffer from impaired function such as difficulty with speech and eating. A less obvious but often of grave concern is the inability to express emotion on the affected side. This loss of nonverbal emotional communication (e.g. patient cannot register pleasure, laughter, surprise, interest and worry; the patient tends to sit with hand over the affected side of face) can be extremely bothersome

and may even lead to social isolation. Therefore, in order to minimize the potential for neurological damage, its possible recurrence, and social implications, it is imperative that the diagnosis of the cause for facial asymmetry (Table 18.5) and weakness be established quickly.

## DIFFERENTIAL DIAGNOSIS

### Common

- Bell's palsy (HSV-1, CMV, EBV, rubella, and mumps)
- Cerebrovascular accidents (stroke)
- CNS infections (bacterial, TB, abscess, malignant otitis media)
- CNS tumors (posterior fossa tumors, acoustic neuroma)
- Diabetic neuropathy
- Head trauma (fractures of the temporal bone).

### Occasional

- Ramsay Hunt syndrome
- Guillain-Barré syndrome (GBS)
- Infections (HIV, cerebral malaria, Lyme disease, chickenpox)
- Tumors invading temporal bone (cholesteatoma).

### Rare

- Infections (tetanus, leprosy, poliomyelitis, diphtheria)
- Multiple sclerosis (MS)
- Myasthenia gravis
- Motor neuron disease
- Sarcoidosis
- Metastasis to temporal bone (from carcinoma breast, bronchus, prostate)
- Neoplasm of base of the skull or parotid gland
- Carcinomatous or leukemic meningitis
- Surgery of mastoid, parotid
- Melkersson-Rosenthal syndrome (MRS: *vide infra* ↓↓).

## INVESTIGATIONS—GENERAL

### CBC

- Leukocytosis in infection.
- May be helpful to rule out lymphoproliferative malignancies such as lymphocytic leukemia, the initial manifestation of which may be peripheral facial palsy.

### Blood Glucose

- To evaluate for diabetes mellitus.

### VDRL

- Indicated in neurosyphilis.

### CXR

- To exclude sarcoidosis or to rule out TB in selected patients before treating with steroids.

## INVESTIGATIONS—SPECIFIC

### CT Skull

- CT scan of the temporal bone for evidence of temporal bone fracture.
- Associated anomalies of the external ear, middle ear, inner ear, etc. can be assessed.

### MRI with Gadolinium

- Generally indicated in patients with atypical features such as:
  - Hearing loss
  - Multiple cranial nerve deficit
  - Signs of limb paresis or sensory loss
  - Lesion suggesting a posterior fossa lesion as the cause of CN VII palsy
  - To exclude neoplasms, stroke, MS, or other structural lesions.

### CSF

- Indicated only in inflammation, granuloma, or malignancy is a consideration.
- A mild pleocytosis of the CSF may be seen in Bell's palsy.



**EMG/NCS**

- To predict recovery, but not needed for diagnosis; most informative when at least three weeks have elapsed after the onset of facial palsy.

**Lyme Titer**

- Lyme disease serology, i.e. enzyme immunoassay (EIA) or immunofluorescent assay (IFA); ELISA for Lyme disease; especially in endemic areas.

**Serum Calcium and Angiotensin-converting Enzyme Levels**

- If sarcoidosis is suspected; these levels are high in sarcoidosis.

**CLINICAL NOTES**

- Careful observation of the patient's face during conversation and at rest almost always reveals facial weakness. Additionally, the face may 'droop' on the side of lesion. Inspection of the face can also include overall muscle function during speech and expression. Occasionally blepharospasm due to facial nerve misdirection (synkinesis), or hemifacial spasm due to inflammatory lesions, or posterior fossa tumor may be noted
- History is reviewed for mode of onset, associated symptoms, ear infection, herpes zoster, tick bite, facial trauma, relevant surgery, and systemic diseases such as diabetes mellitus, hypertension, and malignancy
- **Pregnancy and facial palsy**—Reports have shown that during pregnancy the incidence of Bell's palsy—including facial diplegia, and recurrent LMN facial paralysis in successive pregnancies—is increased significantly compared to nonpregnant women; most cases of Bell's palsy occur in the third trimester or early puerperium; onset is acute and painful<sup>3-5</sup>
- When suspecting lyme disease in the absence of skin lesions (erythema migrans), ask about travel and residence history, and carefully review other signs and symptoms (fever, arthralgia, lymphadenopathy, neuropathy, etc.)
- Associated symptoms such as hyperacusis, deafness, and abnormality of taste, salivation, and facial pain, etc. point to different sites of facial nerve lesions (Table 18.1)
- Onset—Acute onset is common with Bell's palsy, diabetic neuropathy, TIA, CVA, pregnancy, and trauma to facial nerve. CNS infection, abscess, acoustic neuroma, and brain tumor have subacute or gradual onset
- Is there associated hemiparesis or hemiplegia? Presence of such associated neurological deficit of acute onset favors CVA or subdural or extradural hematoma. If hemiplegia or hemiparesis of acute onset is present on the contralateral side, then brainstem thrombosis or hemorrhage must be considered. If the deficit is gradual in onset, and on one side, consider a brain tumor, abscess, or brain degenerative disease
- Evaluation of facial muscle innervated by CN VII such as—wrinkling of the forehead (frontalis), closing the eyes tightly (orbicularis oculi), closing the lips tightly/whistling (orbicularis oris), pulling back the corners of the mouth as in smiling (buccinator), and wrinkling the skin of the neck/frowning (platysma) - help to decide whether UMN or LMN type of facial weakness is present (Table 18.2)
- A careful neurological examination may detect focal deficit such as taste sensation in the anterior 2/3rd of the tongue (lost in LMN type), corneal reflex, plantar response (lost in LMN type), evidence of cerebellar signs and CN VIII involvement (affected in acoustic neuroma)
- Unilateral or bilateral lesions can be tested by having the patient retract one corner of the mouth at a time, winking one eye at a time, and

**Table 18.1:** Localization of facial nerve lesion

Site	Causes	Features
Cortex or brainstem-Supranuclear lesion: (above the facial nucleus)	Cerebral infarction Tumor Multiple sclerosis	Contralateral paralysis of lower facial muscles with relative preservation of upper muscles.
Pons (nuclear or fascicular lesion)	Pontine infarct Basilar artery aneurysm Tumor Sarcoid Multiple sclerosis Vasculitis Syringobulbia	<i>Millard-Gubler syndrome</i> ; <sup>#</sup> <i>Foville's syndrome</i> . <sup>##</sup>
CP angle (peripheral nerve lesion)	Acoustic neuroma Meningioma Secondary neoplasm	Ipsilateral facial monoplegia; loss of taste to anterior 2/3rd of tongue due to involvement of nervous intermedius; impaired salivary and tear secretion, hyperacusis (if CN VIII is not affected); additional CNs may be involved: deafness, tinnitus, vertigo (CN VII), sensory loss over face and absence of corneal reflex (CN V); ipsilateral ataxia (cerebellar peduncle).
Internal auditory canal facial canal, petrous temporal bone)	Bell's palsy Ramsay Hunt syndrome Globus tumor Trauma	Same as above except CNs other, i.e. than CN 7th, 8th palsy: hyperacusis due to paralysis of stapedes muscle; loss of taste from anterior 2/3rd of tongue.
Stylomastoid foramina (skull base or within the face)	Bell's palsy Parotid gland tumor Mumps GBS Sarcoidosis Trauma	Facial paralysis of all muscles; taste and lacrimation preserved.

<sup>#</sup> *Millard gubler syndrome*—due to occlusion of the penetrating branches of the basilar artery in the pons. Its features are: lateral rectus palsy — cranial VI; ipsilateral facial paralysis — cranial VII; and contralateral hemiplegia; often accompanied by contralateral sensory loss — light touch and proprioception - due to medial lemniscal damage. However, this is not part of the defined syndrome.

<sup>##</sup> *Foville's syndrome*—due to occlusion of the perforating branches of the basilar artery in the region of the pons. Its features are: unilateral facial palsy; paralysis of conjugate gaze towards the affected side; and contralateral hemiplegia.

elevating one eyebrow at a time. UMN lesion is usually unilateral as in CVA and neoplasm and rarely bilateral as in GBS and MS. LMN lesion may be unilateral or bilateral (Table 18.3)

- *Facial myokymia* is a rare form of involuntary movement affecting the facial muscles. It is clinically defined as continuous twitching of small bands or strips of muscles that give an undulating or rippling appearance to overlying skin, descriptively called as 'bag of worms'

appearance. It is an important physical sign, as it is most often seen in cases of multiple sclerosis and with neoplastic and inflammatory lesions of the brainstem, and if noted makes brain imaging (MRI) mandatory

- *Mimic palsy*, also known as *emotional facial palsy* (EFP) refers to weakness or abolition of facial movements during emotions like smiling or weeping, while voluntary movements do not show any deficit. EFP has been described in

**Table 18.2:** Difference between UMN and LMN type of CN VII palsy

<i>UMN type</i>	<i>LMN type</i>
<ul style="list-style-type: none"> <li>• Upper face escapes; only lower face affected, i.e. eyes can be closed, forehead wrinkled but teeth cannot be shown with weakness of lips and buccinator muscles</li> <li>• Emotional movement retained. In bilateral UMN lesions whole face is paralyzed and emotional movements are also affected</li> <li>• Bell's phenomenon*—absent</li> <li>• Facial muscles—not atrophied</li> <li>• Taste sensation—preserved</li> <li>• Corneal reflex—present</li> <li>• Hemiplegia—usually associated with ipsilateral hemiplegia or hemiparesis or monoplegia</li> <li>• Plantar response—extensor on the paralysed side of the face</li> <li>• Examples—CVA, CNS neoplasms, MS, syringobulbia, motor neuron disease</li> </ul>	<ul style="list-style-type: none"> <li>• Whole face is involved on one side</li> <li>• Emotional movements are lost</li> <li>• Bell's phenomenon*—present</li> <li>• Facial muscles—fasciculations/atrophy on the affected side may be present</li> <li>• Taste sensation—may be lost</li> <li>• Corneal reflex—lost</li> <li>• Hemiplegia—may be an isolated phenomenon; and if associated with hemiplegia, it is always crossed</li> <li>• Plantar response—flexor on the paralysed side of the face; may be extensor on the opposite side</li> <li>• Examples—Bell's palsy, acoustic neuroma, GBS, Lyme disease</li> </ul>

\* Bell's phenomenon, i.e. if the patient tries to close his affected eye, the eyeball turns upwards and inwards.

**Table 18.3:** Causes of LMN facial weakness: unilateral and bilateral

<i>Unilateral facial weakness</i>	<i>Bilateral facial weakness (facial diplegia)</i>
<ul style="list-style-type: none"> <li>• Bell's palsy</li> <li>• Ramsay Hunt syndrome</li> <li>• Diabetes mellitus</li> <li>• Unilateral parotid disease: infection, stone, tumor, sarcoidosis</li> <li>• Unilateral otitis media</li> <li>• HIV</li> <li>• Lyme disease</li> <li>• Leprosy</li> <li>• Acoustic neuroma, meningioma</li> <li>• Cholesteatoma</li> <li>• Trauma: Petrous fracture</li> <li>• Surgery on mastoid, parotid gland</li> </ul>	<ul style="list-style-type: none"> <li>• Bilateral Bell's palsy</li> <li>• Bilateral parotid disease</li> <li>• Bilateral otitis media</li> <li>• HIV</li> <li>• GBS</li> <li>• Sarcoidosis</li> <li>• Leprosy</li> <li>• Postdiphtheritic palsy</li> <li>• Poliomyelitis</li> <li>• Leukemia</li> <li>• Melkersson syndrome, i.e. recurrent facial palsy with facial edema, unilateral or bilateral; and lingua plicata (scrotal tongue)</li> <li>• Möbius syndrome, i.e. facial paresis with ophthalmoplegia</li> <li>• Myasthenia gravis (not due to facial palsy)</li> <li>• Myotonic dystrophy</li> </ul>

association with lesions of anterior part of frontal lobe, lesions in the neighborhood of optic thalamus, Parkinson's plus syndrome and postencephalitic parkinsonism.

- ACN VII palsy (Bell's palsy) is the most common cranial nerve lesion and is the most common neurologic manifestation of sarcoidosis.<sup>6</sup>

## RED FLAGS

- With *bilateral facial palsy*, although very rare, it's important to rule out all other possible diagnoses for facial weakness, including UMN and LMN disorders, with thorough diagnostic tests (Table 18.4).

**Table 18.4:** Etiology for bilateral facial weakness

<i>Bilateral nuclear lesions: Pontine</i>
• Infarction
• Hemorrhage
• Multiple sclerosis, vasculitis
• Tumor
• Infection
• Syringobulbia
• Motor neuron disease
• Möbius syndrome, i.e. facial paresis with ophthalmoplegia
<i>Bilateral infranuclear lesions:</i>
• Bell's palsy
• GBS
• HIV
• Poliomyelitis
• Postdiphtheritic palsy
• Bilateral parotid disease
• Bilateral otitis media
• Leukemia
• Melkersson syndrome, i.e. recurrent facial palsy with facial edema, unilateral or bilateral; and lingua plicata (scrotal tongue)
<i>Muscle disease:</i>
• Myasthenia gravis
• Myotonic dystrophy
• Fascioscapulohumeral dystrophy

**Table 18.5:** Differential diagnosis of altered facial contour

• Trauma, burns, contractures
• Hemiatrophy (e.g. localized scleroderma, Parry-Romberg syndrome)
• Hemihypertrophy
• Lipodystrophy
• Unilateral postural edema
• Paget's disease, fibrous dysplasia
• Massive parotid gland swelling
• Acromegaly
• Cushingoid faces (moon face)
• Micrognathia
• Congenital — absence of condyle of mandible

- *Bilateral facial palsy* seen in *pregnancy* may be a sign of serious underlying disease. Some authors suggest that Bell's palsy increases the risk of hypertension and toxemia of pregnancy, whereas the pregnant state, in turn, may affect the course and severity of disease.<sup>7</sup>
- Peripheral facial palsy has been considered as a possible neurological complication of the early stages of HIV infection. In the early stage

of HIV, paralysis can be directly due to the viral infection. In later stages paralysis is more likely to be associated with the opportunistic infections or tumors associated with severe immune deficiency.<sup>8</sup>

- Dissatisfaction with facial appearance seems to be a factor in many suicides. In a patient with facial asymmetry (Table 18.5), negative coping strategies may include avoidance of social contact, alcohol misuse, and aggression. It is dangerous for the physician to dismiss a complaint of this type or labelling these patients as 'psychiatric'.<sup>9</sup>

## SELECTIVE GLOSSARY

**Melkersson-Rosenthal syndrome**—MRS is an uncommon condition of unknown cause. Several factors, such as infection, autoimmunity, neurotropic factors, atopy, and hypersensitivity to food additives have been implicated in the pathogenesis, but none of them are proven. An autosomal dominant inheritance with variable expression has been proposed in some cases of MRS.

Although early manifestations of the syndrome can start at any age, MRS generally develops at the end of the second decade of life. The classical triad includes recurrent orofacial edema involving predominantly the lips (macrocheilitis), peripheral facial palsy and scrotal tongue, although it is accepted that the presence of two manifestations is sufficient to make the diagnosis. Facial palsy can be unilateral or bilateral; may tend to be recurrent to such an extent that it's sometimes described as intermittent. Recurrences don't follow any pattern—each recurrence can be on the same side, alternating side, or bilateral. Disturbances of salivary, lacrimal and nasal secretion, disorders of taste and vision, migraine, and febrile symptoms occasionally accompany the condition. MRS is an unusual cause of facial

swelling that can be confused with angioedema. Diagnosis of this syndrome can easily be missed, as the obvious symptoms may look like Bell's palsy. However, unlike MRS, Bell's palsy recurrences tend to be separated by wide time spans.

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## CHAPTER

# 19

## Facial Swelling

### SYNOPSIS

*Facial swelling*, i.e. swelling of the central portion of the face—known as *facial edema*—is a condition wherein there is fluid and/or excess subcutaneous fat accumulation in the face.\* It can be localized or generalized, and may even sometimes spread to the neck and upper arms. Sometimes, it precedes onset of either peripheral or generalized edema. If the facial swelling is mild, it may be difficult to detect; occasionally the patient, or usually someone who is familiar with patient's appearance may report it before it is noticed during assessment. Most of the time facial swelling is not a cause for alarm, but when the swollen area is inflamed, or there is difficulty in breathing, or the swelling does not decrease over time, it becomes a cause of concern. Many causes are due to infection and allergy, but it may be a sign of systemic disease. However, the patient usually presents because of the abnormal facial features, expressions, and even disfigurement.

\* Disorders of only facial subcutaneous and soft tissues are considered; those related to other facial organs (eyes, nose, jaws, vascular, neoplasms, etc.) are excluded.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Obesity (BMI > 30 kg/m<sup>2</sup>)
- Angioedema (hereditary, drug allergy, e.g. ACE-inhibitors)
- Systemic disorder (CHF, acute glomerulonephritis, nephrotic syndrome, uremia, hepatic failure)
- Insect bites, stings
- Infection (cellulitis, including orbital cellulitis; erysipelas of the face)
- Mumps
- Sinusitis (maxillary, frontal)
- Dental abscess
- Myxedema
- Cushing's syndrome (iatrogenic, i.e. exogenous steroid induced)
- Trauma
- Burns.

#### Occasional

- Hypoproteinemia (in hepatic, renal, and nutritional disorders)
- Severe anemia of chronic disease
- Trichinosis



- Salivary gland calculus
- Ludwig's angina.

#### Rare

- Cushing's syndrome (noniatrogenic)
- Superior vena caval syndrome
- Cavernous sinus thrombosis
- Autoimmune disorders (dermatomyositis, scleroderma, Sjögren's syndrome, SLE)
- Extremes of temperature (frostbite, sun burn)
- Kaposi sarcoma
- Burkitt's lymphoma
- Morbihan's disease<sup>1,2</sup> (*vide infra* ↓↓).

### INVESTIGATIONS—GENERAL

#### CBC

- Leukocytosis in infections, cellulitis, dental abscess.
- Eosinophilia in allergic disorders, trichinosis.
- Anemia of iron, folate deficiency in chronic disease.

#### ESR

- Elevated in infection, and autoimmune disorders.

#### Urinalysis

- Proteinuria, hematuria, and RBC casts in renal disease.

#### Plasma Protein

- In hypoproteinemic edema, total plasma protein level is less than 5 g/dl and the plasma albumin content is below 1.5-2.5 g/dl.

#### Urea, Creatinine

- Elevated in renal failure.

#### Blood Glucose

- In diabetic patients, especially in Type 1 DM, insulin therapy may be associated with the development of transient edema.

#### CXR

- Pulmonary opacity, hilar lymphadenopathy, mediastinal tumor, aortic aneurysm, etc. may be evident, causing superior vena caval obstruction
- Bronchogenic carcinoma may lead to 'ectopic ACTH syndrome', causing non-iatrogenic Cushing's syndrome.

#### X-ray PNS

- Opacity or a fluid level may be evident in the involved sinus; bony erosion may suggest malignancy.

### INVESTIGATIONS—SPECIFIC

#### TFTs

- Elevated THS values indicate hypothyroidism, cretinism.

#### ANA

- To screen for underlying autoimmune disorder.

#### Parotid Sialography

- To detect any abnormality and obstruction of the Stensen's duct.

#### CT/MRI Brain

- For evidence of cavernous sinus thrombosis, Cushing's syndrome (pituitary microadenoma secreting ACTH tumor).
- In patients with CNS signs and symptoms due to trichinellosis.

#### CT/MRI Lungs, Abdomen

- To confirm CXR lesions, and adrenal adenoma.

#### CT/MRI PNS

- For detailed evaluation of PNS; obscure lesions such as polyps, tumors may be evident causing recurrent sinusitis and facial edema.

### Plasma/Urinary Cortisol

- In Cushing's syndrome, especially in non-iatrogenic type.

### Muscle Biopsy (Bx)

- To confirm trichinella infestation.

## CLINICAL NOTES

- Evaluation of facial swelling requires consideration of onset, severity, location, duration, aggravating and ameliorating factors
- Other causes of facial edema, such as edema secondary to congestive heart failure, renal insufficiency, hepatic insufficiency, or venous stasis disease must be excluded
- Acute onset associated with pain and tenderness is usual with infective and allergic lesions, whereas gradual onset indicate renal, endocrine, and autoimmune disorders
- Recurrent painful swelling of the affected parotid gland at meals and regressing afterwards is very characteristic of obstruction to the duct of the gland by a stone
- In patients with salivary gland enlargement, inquiry about symptoms of rheumatologic disease or 'sicca syndrome' (dry eyes, dry mouth) is important
- A unilaterally enlarged painless parotid gland with a facial palsy suggests parotid tumor; bilateral involvement may indicate lymphoma, sarcoidosis, and Sjögren's syndrome
- Periorbital puffiness—Its common causes are stated in Table 19.1
- *Drugs*—History of steroid therapy and allergic reactions to NSAIDs, antibiotics, blood products, and vaccines may result in periorbital or facial edema.

## RED FLAGS

- Any facial swelling involving deep facial spaces, as evidenced by fever, trismus,

**Table 19.1:** Differential diagnosis of periorbital edema

- Allergic
  - Angioedema, insect bite, sting (i.e. hives), contact eczema
- Infections
  - Bacterial—cellulitis, sinusitis, cavernous sinus thrombosis, anthrax (cutaneous)
  - Viral—infectious mononucleosis
  - Parasitic—trichinosis
- Eye—infection—blepharitis, dacryocystitis
- Iatrogenic
  - Drug induced—steroids, hormones
- Systemic edema
  - Nephrotic syndrome
  - Anemia—severe
  - Hypoproteinemia
  - Subcutaneous emphysema
- Endocrinologic
  - Hypothyroidism
  - Graves' orbitopathy
  - Cushing's syndrome
- Autoimmune disorder
  - Dermatomyositis
  - SLE
- Trauma
  - Fracture of nasal, sinus, orbital bones
  - Foreign body
- Neoplastic
  - Retinoblastoma
  - Kaposi's sarcoma
  - Burkitt's lymphoma
  - Superior vena cava syndrome
  - Secondary tumors (eyelid, eyeball, nose, paranasal sinuses, brain)
- **Periorbital xanthelasmata**
- Familial
  - Angioneurotic edema (i.e. C1 inhibitor deficiency)
  - Melkersson-Rosenthal Syndrome (i.e. neurological disorder characterized by facial swelling, especially of the lips).

elevation of the tongue, or ophthalmoplegia (e.g. facial cellulitis, angioedema, Ludwig's angina) could be dangerous (causing asphyxia); close monitoring/referral is indicated

- Mediastinal lesion, e.g. bronchogenic carcinoma may present as facial edema due to compression/obstruction to the superior vena cava
- In lupus erythematosus, dramatic periorbital edema and erythema without any

evidence of other significant cutaneous or systemic involvement, though unusual, could be the sole manifestation of cutaneous lupus erythematosus. Therefore, every patient with persistent periorbital edema should undergo histologic and immunofluorescent evaluation, and lupus erythematosus should be included in the differential diagnosis.<sup>3</sup>

- Unilateral facial swelling, involving orbital region, may signal cavernous sinus thrombosis, especially in immunocompromised and diabetic patients.

### SELECTIVE GLOSSARY

**Morbihan's disease**—It is a rare condition characterized by chronic persistent erythema and edema of the upper half of the face. Such conditions have also been designated as chronic

lymphedema or solid persistent facial edema in acne or rosacea. The chronic course, absence of serological abnormalities and nonspecific histopathological features, as well as resistance to therapy is the most important diagnostic criteria of this disease. Cases remain difficult to treat and can challenge afflicted patients both cosmetically and psychologically.

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## CHAPTER

# 20

## Fever of Unknown Origin

### SYNOPSIS

*Fever or pyrexia* is a common presentation in most fields of medical practice. It is usually associated with benign transitory infection. In most patients, the epidemiological guidelines and incidence greatly help in the evaluation of the underlying cause, generally within a week, or the patient recovers spontaneously. It is only when fever prolongs, and the cause remains unknown, that it causes a diagnostic challenge, and fever of such cases is labeled as *Fever of Unknown Origin* (FUO). However, modern diagnostic and imaging techniques enable early detection of a number of occult diseases such as neoplasms, lymphomas, and connective tissue disorders in patients previously thought to have FUO.<sup>1</sup>

Several authors\* have devised criteria for defining a FUO. Petersdorf and Beeson defined FUO in adults as:

- Temperature higher than 38.3°C (> 101°F) on several occasions (i.e. fever does not have to be continuous or daily, but occurs in majority of days of the illness)

- Fever lasting more than three weeks
- Failure to reach a diagnosis despite one week of inpatient investigation.

The criteria of three weeks were chosen because it eliminates the prolonged but self-limiting viral and bacterial diseases, and allows sufficient time for appropriate initial investigations to be completed. However, “over the past 40 years, health care has shifted from the inpatient to the ambulatory setting. As a result, it has now become widely accepted that the requirement for a one week evaluation in hospital be modified so that evaluation may now be completed in an outpatient setting”.<sup>2,3</sup>

In most cases the cause of fever becomes evident within two weeks, thus underlying the common axiom that FUO is more often an unusual presentation of a common disease rather than a common presentation of a rare disease. Conversely, failure to utilize clinical findings correctly, delay in ordering appropriate tests, and misinterpretation of test results have all contributed to missed diagnoses.

Some experts have argued for a more comprehensive definition of FUO that takes into account medical advances and changes in disease states, such as the emergence of HIV infection and

\* Petersdorf and Beeson (1964); Durrack and street (1991); Lohr and Hendley (1977).

an increasing number of patients with neutropenia (neutrophil count < 500/microliter). Others contend that altering the definition would not benefit the evaluation and care of patients with FUO.<sup>4-6</sup>

FUO demands great tenacity for constant observation, frequent careful physical examination for the evidence of newer signs, avoidance of unnecessary investigations at early stages, and above all an excellent rapport with the patient. "It is in the diagnosis of a febrile illness that the science and art of medicine come together".<sup>7</sup> With such an approach, FUO will but be a challenge in a minority of patients. However, about one-third of patients have no diagnosis at the end of the work up, and for them the prognosis is usually good. There is no algorithm to know which tests to order. Focused history and detailed physical status give important clues to decide about additional laboratories testing. An empirical treatment is justified only in case of vital risk.

## DIFFERENTIAL DIAGNOSIS

### Common

- Tuberculosis (TB, especially extrapulmonary and miliary)
- Abscesses (intra-abdominal, retroperitoneal, and pelvic)
- Extraintestinal amebiasis<sup>8</sup>
- Chronic active hepatitis
- Hodgkin's lymphoma, non-Hodgkin's lymphoma
- HIV infection (pyogenic; atypical mycobacterial; fungal: *Pneumocystis carinii*, candidiasis; viral).

### Occasional

- Severe acute respiratory syndrome (SARS)
- Infective endocarditis (IE)
- Brucellosis
- Leptospirosis
- Kala-azar
- Acute leukemia

- Sarcoidosis
- Temporal arteritis
- Rheumatoid arthritis (RA), Still's disease
- Deep venous thrombosis (DVT).

### Rare

- Viral (CMV, Epstein-Barr virus, Herpes Simplex)
- Carcinoma (hypernephroma, Hepatoma, colon carcinoma)
- Metastatic cancers (disseminated carcinoma)
- Connective tissue disorders (SLE, PMR, PAN)
- Drug fever
- Endoprostheses, grafts, stents<sup>9-11</sup>
- Hereditary periodic fever syndromes (Familial Mediterranean fever).

## INVESTIGATIONS—GENERAL (TABLE 20.1)

### CBC, PS.<sup>†</sup>

- Anemia will be revealed in a variety of disorders such as malignancy, connective tissue disorders; leukocytosis in many infective, inflammatory diseases, and leukemia; low platelets in leukemia; malarial parasites; abnormal WBCs in leukemia; and atypical lymphocytes in infectious mononucleosis, HIV, viral hepatitis can occasionally help in the diagnosis.

### ESR

- A markedly raised ESR is common in TB, malignancy, inflammatory and connective tissue disorders.

### Culture

- Blood (infective endocarditis), urine, and abnormal fluid collection or secretion such as from throat, urethra, cervix, abdominal, pleural, and joint space for suspected infection.

<sup>†</sup>Examination by hematopathologist may be indicated in suspected hematologic malignancy.

**Table 20.1:** Minimum diagnostic work-up to qualify as FUO\*\*

- Comprehensive medical history
- Repeated physical examination
- Complete blood count and differential
- Microscopic examination of blood film, routine blood chemistry (including lactic dehydrogenase, bilirubin, and liver enzymes)
- Blood sedimentation rate
- Urinalysis and microscopy
- Chest radiography
- Blood and urine culture (before initiation of antibiotic treatment)
- Antinuclear antibodies
- Rheumatoid factor
- Serology for CMVs and Epstein-Barr virus
- HIV antigen and antibody tests
- Hepatitis serology (if abnormal liver enzyme tests result)
- Angiotensin converting enzyme
- CT scan of abdomen
- Q fever serology (if exposure risk factors exist)
- Examination for specific endemic infectious disease in returning travellers or persons living in such geographic areas (e.g. systemic leishmaniasis in India, Mediterranean area, etc.)
- Tuberculin test
- Evaluation of any abnormal symptoms and findings

\*\* Source: Siegenthaler Walter. Siegenthaler's Differential Diagnosis in Internal Medicine From Symptoms to Diagnosis, Thieme, 1st English ed. Chapter-4-Fever of Unknown Origin-Table 4.2 - Minimum Diagnostic work-up to qualify as FUO, p. 114.

### Urinalysis

- WBCs in infection; granular or red cell casts in renal inflammation; hematuria in infection, endocarditis, hypernephroma, and blood dyscrasias. Proteinuria suggests renal disease.

### PPD or Mantoux Test

- Should be done in all cases of FUO. Negative results are reported in miliary TB, sarcoidosis, Hodgkin's disease, AIDS, or malnutrition.

### CXR

- Usually detects infiltration, consolidation, effusion, masses, and lymphadenopathy even before they are clinically evident.
- TB—Parenchymal or miliary, primary and metastatic malignancy, lymphoma, sarcoids,

fungal lesions, and *Pneumocystic carinii* pneumonia may be suspected.

### Plain X-ray of Bones

- In osteomyelitis, periosteal reaction and sequestration develop 10-15 days later; for earlier diagnosis radionucleotide bone scan is preferred.

### US Abdomen, Pelvis

- To rule out intra-abdominal masses or abscesses of liver, spleen, kidney, and pelvic organs.

### LFT

- Hepatic involvement in FUO is common; significant elevated values of transaminase levels indicate hepatitis; elevated alkaline phosphatase levels point to infiltration of the liver.

### Sputum

- Gram's stain, AFB, and culture.

### Stool Microscopy and Culture

- Ova, parasites, cysts, and occult blood on microscopy.

### Blood Glucose

- To detect diabetes mellitus in previously undetected patients.

### CSF

- In suspected cases with pyogenic, tubercular meningitis, and viral encephalitis.

## INVESTIGATIONS—SPECIFIC

### HRCT Abdomen/Pelvis

- Recommended as one of the first investigations in FUO in the majority of patients with symptoms suggesting an intraabdominal abscess and lymphoma; in patients with suspected retroperitoneal tumors or infections, or those with abnormal



LFTs. Even in asymptomatic patients with FUO, a normal CT abdomen is very helpful in ruling out serious intra-abdominal or retroperitoneal pathology.

### Nuclear Imaging

- Between Gallium (Ga) 67, Technetium (Tc) 99 m, or indium (In) 111, Tc 99 m is the tracer of choice in localizing a potential infection or inflammatory focus
- 18F-fluorodeoxy glucose positron emission tomography, i.e. (18) F-FDG PET—Osteomyelitis can be diagnosed with a high degree of certainty. Negative findings on (18) F-FDG PET essentially rule out orthopedic prosthetic infections. In patients with noninfectious inflammatory diseases, (18) F-FDG PET is of importance in the diagnosis of large-vessel vasculitis and seems to be useful in the visualization of other diseases, such as inflammatory bowel disease, sarcoidosis, and painless subacute thyroiditis. In patients with tumor fever, diseases commonly detected by (18) F-FDG PET include Hodgkin's disease and aggressive non-Hodgkin's lymphoma, and also colorectal cancer and sarcoma.<sup>12,13</sup>

### FNAC and Directed Biopsies

- A temporal artery biopsy (Bx) should be considered in elderly patients with FUO
- Color duplex ultrasonography of the temporal arteries may be a helpful alternative to temporal artery biopsy
- Lymph node biopsy will rule out lymphomas, TB, metastatic carcinomas, and mycotic infections
- Liver biopsy will detect granulomatous or metastatic lesions
- Bone marrow biopsy can diagnose leukemia, lymphomas, carcinoma, and granuloma.
- LD bodies may be noted in lymph node, spleen, or bone marrow aspirate in patients with kala-azar.

### Leg Doppler Imaging

- For evidence of superficial or deep venous thrombosis.

### Echocardiography

- Transthoracic echocardiography (TTE)—For evidence of infective endocarditis, to detect vegetations on the valve cusp, especially if blood cultures are negative.
- Transesophageal echocardiography (TEE)—Considered to investigate suspected pacemaker lead infection in patients with negative transthoracic echocardiography.<sup>14</sup>

### Serological Tests

- May be helpful in disorders such as viral hepatitis (anti-HAV IgM, HBsAg, anti-HCV); HIV (ELISA, Western Blot); infectious mononucleosis (heterophil test); antibodies against CMV infection, amoebiasis, brucellosis, toxoplasmosis; salmonella (Widal titer); and collagen vascular diseases (ANA, RF, Antineutrophil cytoplasmic antibody-ANCA).

### HRCT Chest

- Miliary TB, which can be missed on normal CXR, is better defined by HRCT.

### Endoscopic Procedures

- Bronchoscopy, mediastinoscopy, EGD, retrograde cholangiography, colonoscopy, transrectal sonography, or laparoscopy may help direct visualization, and biopsy procedures when organ specific manifestations are present.

## CLINICAL NOTES

- The first step should be to confirm the history of fever, its documentation, and *exclusion of habitual, factitious, or drug-induced fever* (see text below)
- Fever patterns such as intermittent, relapsing,

sustained may prove to be helpful but rarely diagnostic; it may aid in diagnosing cases of tertian or quartan malaria, or Hodgkin's disease (with Pel-Ebstein fever characterized by 5-10 days of fever alternating with 5-10 days of afebrility)

- A single record of temperature in a febrile patient gives very little information. In all cases of fever, a serial record of temperature is essential; four-hourly in acute cases and eight-hourly in all other cases. A simultaneous record of pulse rate and respiration gives additional information that may be clinically useful
- The duration of fever prior to seeking medical help may give some clues. The longer the duration of the fever, the less likely there is an infectious etiology; if it is of month's duration, then autoimmune or malignant disorders are the possibilities; when it's more than a year or so, then granulomatous diseases are the probabilities
- *Naproxen test*<sup>15</sup>: The response to fever to naproxen sodium may be helpful in that fever due to solid tumors and many rheumatologic diseases (most notably Still's disease) usually subside promptly, while fever due to other causes may persist
- History of recent travel (malaria, SARS); pets, animal and insect contacts (toxoplasmosis, brucellosis, leptospirosis, Lyme disease); occupation (brucellosis in abattoir workers, anthrax in leather workers); and recent contact with persons exhibiting similar symptoms (viral hepatitis, TB) are important aids in the diagnosis
- The family history should also be carefully elicited for hereditary causes of fever, such as familial Mediterranean fever. Diseases such as rheumatic fever, tuberculosis, lymphoma, etc. in other family members must be enquired
- *Drug-induced fever* (antihistamines, antibiotics,

antineoplastics, atropine and its compounds, barbiturates, iodides, phenytoin, quinidine) must be considered in patients who are taking medications, including OTC drugs, because elimination of the offending agent may solve the problem and eliminate the need for extensive investigations. If fever persists beyond 72 hours of stopping all possible offending drugs then the likelihood of fever being drug-induced is markedly reduced

- History of high risk sexual activity and IV drug abuse need screening for HIV, viral hepatitis, and infective endocarditis. History of alcohol abuse indicates cirrhosis, and hepatoma
- A past history of intermittent illness over a period of years involving multiple organ systems suggests the possibility of connective tissue disease
- Fundoscopic examination may provide the first clue to the diagnosis of tuberculosis if choroid tubercles are demonstrable. Ocular manifestations of systemic diseases such as scleritis, uvulitis in connective tissue disorders may provide clues to the diagnosis of obscure fever. Hence, referral to an ophthalmologist in the early stages of FUO is particularly useful
- Physical examination—Must be thorough and often repeated. Symptoms and signs of common diseases causing FUO are given in Table 20.2
- Fever associated with rash may be a viral exanthem (e.g. rubella, varicella) or a clue to a serious disease (e.g. meningococcemia, thrombocytopenia, erythema multiforme).

## RED FLAGS

- Rule out *habitual hyperthermia*, i.e. exaggerated circadian rhythm, characterized by temperature between 100 and 100.5°F in the afternoon hours; other febrile symptoms (chills, sweats, and tachycardia) are absent and initial tests are normal

Table 20.2: FUO—Common causes

Symptoms and signs	Cause
Skin—Mucous membrane—petechial eruptions, Erythema chronicus migrans, Pruritus	Meningococcemia Lyme disease Hepatitis, Hodgkin's lymphoma, hepatic-tumor
Scalp—Tender cranial arteries, Seborrheic dermatitis	Temporal arteritis HIV
Face—Butterfly rash	SLE
Eyes—Subconjunctival petechial, splinter hemorrhages, Dry eyes	IE
Conjunctiva—Icterus	RA Hepatitis, leptospirosis, hepatic/pancreatic-malignancy
Fundi—Roth spots, Choroidal tubercle, Retinal hemorrhages, infiltrates	IE Miliary TB Leukemia, lymphoma
Oral cavity—Ulcers	SLE
Ears—Ear pain, diminished hearing, tympanic membrane-erythema, effusion	Otitis media, mastoiditis
Neck—Stiffness	Meningitis
Thyroid—Tenderness, Lymphadenopathy	Thyroiditis TB, infectious mononucleosis, lymphoma, sarcoidosis
Hands—Clubbing, Raynaud's phenomenon	IE, SLE, RA
Arms—Drug injection sites	IV drug abuse
Chest—Cough, hemoptysis, dyspnea, consolidation, effusion, rub	TB, lymphoma, malignancy
Cardia—Dental procedure, skin lesion, 'varying' murmurs, conduction disorder, rub	IE, pericarditis
Abdomen—Tenderness, guarding, hepatosplenomegaly, mass	Hepatitis, cholecystitis, abscess, kala-azar, infective endocarditis, malignancy
Scrotum—Swelling, tenderness, mass	Orchitis, seminoma, TB, epididymitis
Penis—Discharge, rash, ulcer	HIV
Digital rectal examination—Tenderness, mass	Prostatitis, perianal abscess
Pelvic examination—Discharge, dysuria	Pelvic inflammatory disease
Bones and joints—Pain, tenderness, swelling, restricted movements	RA, PMR, Osteomyelitis, metastatic deposits
Lower extremities—Calf swelling, tenderness, palpable cord	Thrombophlebitis
Back—Tenderness, swelling over spine, restricted painful movements	Spinal TB, Paravertebral/spinal epidural abscess, metastatic deposits
CNS—Altered consciousness, Focal deficit	Encephalitis; TB, cryptococcal meningitis Brain abscess, mass lesion

- Rule out *factitious fever*. Clues to the diagnosis are a patient with medical knowledge or training, inconsistent histories, excessively high temperatures (105°-107°F, which are a rare occurrence), normal pulse and respiratory rates at the time of fever, and rapid defervescence unaccompanied by diaphoresis
- A high index of suspicion of temporal (or giant cell) arteritis, characterized by headache, fever, jaw claudication, visual symptoms, polymyalgia rheumatica, and constitutional symptoms must be maintained, since failure to do so, and to institute appropriate treatment may lead to permanent vision loss
- FUO should be presumed to be secondary to an infection (bacterial, parasitic, fungal, viral, rickettsial, and chlamydial) until proven otherwise because infections cause the majority of FUOs and can be life-threatening
- The diagnosis of TB may be delayed despite a high index of suspicion because of normal CXR, negative skin and sputum test, and inconclusive histopathologic examination. Repeated examination and work-up is indicated in patients with strong clinical suspicion of TB
- A high index of suspicion and familiarity with the rapidly changing epidemiology of SARS is extremely useful in its early diagnosis and minimizing transmission
- Patients who are elderly, immunocompromised, taking steroids or NSAIDs may not show evidence of fever, even in the presence of a severe infection
- Patients who present with rash associated with FUO should have a skin biopsy (Bx) unless the diagnosis is straightforward
- Patients who are immunosuppressed (on corticosteroids, chemotherapy) or who have

altered immune response due to disease (Hodgkin's, HIV), are likely to have fever due to infection caused by atypical organisms.

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## CHAPTER

# 21

## Gait Disorders

### SYNOPSIS

Gait normally means the rhythmic stepping movements to advance in space, i.e. the manner or posture of a person while walking. When a normal person walks (i.e. locomotion), he maintains an upright, erect posture; balancing is easy, i.e. he is able to stand up and remain upright against the force of gravity (equilibrium); the arms swing at the sides; turning is smoothly accomplished; and cyclical stepping movements are well-coordinated\*. The person is able to stand with feet together without falling with eyes open or closed.

The erect posture of the body is governed by four primary antigravity muscle groups: gastrocnemius/soleus group, the quadriceps group, the glutei, and the erector spinae group. These muscles act on the information from the three major sensory systems in the body: the proprioceptive, vestibular, and visual systems.

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\* Gait consists of two phases: stance and swing. In the stance phase the foot is in contact with the floor, and one limb bears all the body weight. In the swing phase the foot is not touching the floor. This phase begins when the toe comes off the floor and ends with the heel strike.

The feedback by these sensory systems is further integrated and modified by brainstem, basal ganglia, cerebellar, and cortical influences. The spinal cord coordinates muscles of locomotion in all the four limbs by its neural circuitry. The cerebellum maintains proper position and balance. The cortex and basal ganglia evoke walking motion and can modify the slow walk to quick pace.

Thus, any lesion at:

- Lower level<sup>†</sup>, i.e. motor system (muscles, nerves), joint/skeletal system, proprioception (sensory) system, visual/ vestibular system, spinal cord
- Middle level, i.e. brainstem, thalamus, basal ganglia, cerebellum
- High level, i.e. cortical frontal lobe system — can lead to gait disorders.

Patients with abnormal gait commonly complain of unsteadiness or imbalance, staggering, unsteady, walking like a 'drunk sailor,' veering, or having a fear of falling, which is generally an expression of difficulty in maintaining

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<sup>†</sup> The anatomical structures that subserve the system of balance and locomotion are divided into low, middle, and high anatomical levels.

upright posture, either while standing (balancing) or walking (gait). In addition, they may complain of stiffness, cramping, numbness, easy fatigability, muscle wasting, foot drag, frequent tripping, or difficulty climbing stairs and rising from a seated position.

Although the physical examination is the key in evaluating balance and gait disorders, history is also important, mainly to delineate onset and temporal pattern and determine whether symptoms are static, worsening, or improving overtime. The work-up depends on the presence or absence of other neurologic signs.

## DIFFERENTIAL DIAGNOSIS

### Common

- Senile gait (i.e. cautious gait)
- ‘Fear-of-falling’ gait<sup>1</sup> (*vide infra* ↓↓)
- Hemiplegic gait (i.e. circumducting, spastic gait-due to unilateral UMN lesion, e.g. stroke; mass lesion, e.g. tuberculoma, tumor; MS; and Brown-Sequard syndrome: *vide infra* ↓↓)
- Antalgic gait (i.e. painful gait due to joint, bone, or muscle lesion; e.g. trauma, previous bone/joint surgery, malunion, septic arthritis, osteomyelitis, OA, and RA)
- Cerebellar gait (i.e. ataxic or wide-based gait due to drugs; e.g. phenytoin, alcohol, cerebellar ischemia, hemorrhage, and acoustic neuroma)
- Vertiginous gait (due to BPPV, labyrinthitis, Ménière’s disease).

### Occasional

- Stepping gait (due to LMN lesion—unilateral or bilateral, e.g. common peroneal nerve palsy, foot drop)
- Festinating gait (due to basal ganglia, extrapyramidal lesion; e.g. parkinsonism).

### Rare

- Scissors gait (i.e. spastic or paraparetic due to bilateral UMN lesion, e.g. cerebral palsy; MS; cervical cord compression)
- Waddling gait (due to proximal muscle weakness, myopathy, myasthenia, bilateral congenital dislocation of the hip)
- Stomping gait (i.e. sensory gait due to dorsal column disease, e.g. Vit B<sub>12</sub> deficiency, tabes dorsalis, HIV myelopathy)
- Magnetic gait (due to normal pressure hydrocephalus, i.e. NPH: *vide infra* ↓↓)
- Psychogenic gait (i.e. Bizarre gait in somatization disorders).

## INVESTIGATIONS—GENERAL

### CBC

- Leukocytosis in bone and joint infection, and megaloblastic anemia in patients with dorsal column disease.

### ESR

- Elevated significantly in inflammatory joint disease, e.g. RA.

### X-ray

- As indicated in bone and joint disorders.

### ECG

- In hypokalemia, ECG may show sinus bradycardia and evidence of hypokalemia (flattening of T waves, U waves in leads II, V2, V3, and V4, and ST segment depression). In hyperkalemia, tall T waves may be seen.

## INVESTIGATIONS—SPECIFIC

### MRI Brain/Spinal Cord

- The most common initial imaging test is a brain/spinal MRI scan. This test enables to



look for structural abnormalities, stroke, or tumors

- Particularly useful to detect tumors of the posterior fossa, brainstem, and MS. Also helpful to exclude other causes of neurological deficit, e.g. arteriovenous malformation, including lesions causing compression of the spinal cord.

### CT Brain

- Useful in acute stroke and to exclude mass lesion.

### CSF

- Leukocytosis in bacterial meningitis, cerebral abscess; eosinophils in helminthic (neurocysticercosis) infection; low glucose in bacterial, TB infection; oligoclonal bands of IgG in MS; and cytology to detect malignant cells.

### Serum Electrolytes

- Hyperkalemia or hypokalemia in familial periodic paralysis
- In patients with hypokalemia, serum potassium level decreases during attacks, but not necessarily below normal
- In patients with hyperkalemia, serum potassium level may increase to as high as 5–6 mEq/l. Sometimes, it may be at the upper limit of normal, and it seldom reaches cardiotoxic levels.

### Muscle Enzymes

- Increased levels of various muscle enzymes such as CK, AST (e.g. muscular dystrophy, polymyositis: *vide infra* ↓↓); in the presence of polymyositis, CK levels can be elevated as much as 50 times the reference level.

### TFTs

- Proximal myopathy is known to occur in hyperthyroidism, and cerebellar ataxia may be seen in hypothyroidism.

### RA factor and ANA

- In autoimmune arthropathies.

### Serum B<sub>12</sub> and Folate Levels

- As indicated in megaloblastic anemia.

### EMG/NCS

- May be informative in inherited peripheral neuropathy (Friedreich's ataxia: *vide infra* ↓↓, Charcot-Marie-Tooth disease) or myopathy.

### Genetic Testing

- DNA testing for inherited neuropathies, Friedreich's ataxia (FA), and muscular dystrophy.

### Drug Screen

- Especially for anticonvulsant medications. Blood alcohol levels if intoxication is suggested.

### Muscle Biopsy

- In muscular dystrophy, polymyositis, and connective tissue disease.

## CLINICAL NOTES

- Gait abnormality can indicate a serious medical emergency, especially when the problem is associated with any of these additional symptoms:
  - Headache (raised ICP)
  - Nausea or vomiting
  - Decreased alertness
  - Impaired coordination on only one side of the body
  - Recent viral illness/immunization (Guillain-Barré syndrome)
  - Trauma.

A vascular or any lesion causing increased ICP, such as an abscess or a tumor needs to

be urgently treated. It is therefore important to note the mode of onset and progress

- The presence of associated symptoms and signs such as:
  - Tinnitus, deafness, or vertigo suggests Ménière's disease, labyrinthine disease, or eighth nerve lesion;
  - Headache, nystagmus, or papilledema suggest a cerebellar tumor or acoustic neuroma; and
  - Glove and stocking anesthesia with diminished reflexes suggest peripheral neuropathy or tabes dorsalis.
- Acute onset hemiplegic gait with symptoms of raised ICP is mostly due to contralateral stroke or head injury. Acute ataxic gait with cerebellar signs (hypotonia, slurred speech, and nystagmus) may be due to insufficiency/thrombosis of the basilar artery/posterior inferior cerebellar artery; drug toxicity; alcohol abuse; or cerebellar hemorrhage
- Chronic gait disorders are usually due to CNS/spinal mass lesion, infection, nutritional deficiency, substance abuse, or autoimmune disease such as MS
- Medications, e.g. diuretics, statins, steroids are known to cause myopathies leading to progressive weakness and wasting of skeletal muscles, thus resulting in gait disorders. Drugs such as antiepileptics (particularly phenytoin and carbamazepine), antihistamines, benzodiazepines, sedatives-hypnotics, antidepressants, neuroleptics, alcohol, chemotherapy, heavy metal poisoning (e.g. lead, mercury, and thallium), and bromide intoxication are common and reversible causes of gait disorders
- A careful family history should be obtained to determine if an inheritance pattern can be found. Many types of gait disorders are hereditary, e.g. autosomal recessive ataxias such as Friedreich ataxia, ataxia telangiectasia; and autosomal dominant ataxias such as spinocerebellar ataxia, episodic ataxia, etc.) It is therefore important to look for subtle symptoms in family members. Eliciting information by asking questions such as — are there relatives with clumsiness, frequent falling, late walking, early speech therapy, unusual eye movements, deafness, poor handwriting, or other neurological problems, tendency to diabetes mellitus or malignancies—are very helpful to trace the hereditary etiology and genetic pattern
- Observing the patient stand and walk across the room and carefully observing his posture, gait initiation, base width, step rhythmicity, step length, and arm swing may indicate the likely causative lesion (Table 21.1)
- *Tandem walk*: Ask the patient to walk a straight line in tandem, i.e. heel to toe. This may reveal a gait abnormality not previously obvious. It also exacerbates all existing gait disorders, especially associated with vestibular and cerebellar disease. Patients with cerebellar disease (e.g. midline cerebellar vermis lesion) will tend to fall preferentially to the side of the lesion
- Ask the patient to walk on his heels. This can not be done by patients with distal muscle weakness or foot drop (L4 or L5 lesion)
- Ask the patient to walk on his toes. This can not be done by patients with Parkinson's disease, cerebellar disease, or marked soleus or gastrocnemius muscles (S1 lesion)
- A thorough gait assessment should be performed in all older people. An abnormal gait may suggest a remediable risk factor for falls, e.g. difficulty in getting out of a chair without arm support and initiate movement suggests Parkinson's disease or limb-girdle dystrophy. The 'Timed Up and Go' (TUG) test,

Table 21.1: Common gait disorders

<i>Gait</i>	<i>Pattern</i>	<i>Cause</i>
Essential Senile gait	Unsteady; careful; slow; short steps; wide base; stooped posture; diminished arm swing; no rigidity	Age-related without accompanying neuropsychiatric abnormality; diffuse cerebral cortex dysfunction; multi-infract dementia
Hemiplegic	Extended leg; arms flexed; circumduction (i.e. round and forward movement) of the affected leg	Stroke
Paraparetic (Scissor; wooden soldier)	Stiffness (spasticity) of both legs; feet remain on ground	Cerebral palsy; cord compression; MS; syringomyelia
Cerebellar (drunken sailor)	Wide-based; dysmetria; (reeling, unsteady, staggering towards lesion)	Cerebellar lesion; alcoholism; myxedema; MS
Antalgic	Limping; avoidance of bearing full weight on the affected leg; limitation of range of movement due to pain in the extremity	OA of the hip or knee; herniated disk; fracture of any of the bones of the limb; sprained ankle
Stamping (sensory)	High stepping; wide-base; bangs feet down (stamps) clumsily; tends to look at them throughout the cycle (loss of position sense); positive Romberg's sign	Peripheral neuropathy (diabetes mellitus); posterior column lesions, (B <sub>12</sub> deficiency-subacute combined degeneration of the spinal cord, HIV myelopathy); tabes dorsalis
Steppage	Foot drop; high lift to avoid tripping; slaps on floor; unilateral or bilateral	Lateral popliteal nerve palsy; peroneal muscular atrophy; cauda equina tumor; Guillain-Barré syndrome; poliomyelitis; lead intoxication
Festinating (propulsive or retropulsive)	Rigidity; shuffling (short accelerating steps when walking); festination with stopped posture	Parkinson's disease
Waddling	Wide-based; hips tilted alternately (glutei weak); waddling or rolling from side to side; toe-walk; lumbar lordosis; symmetrical	Proximal myopathy (muscular dystrophy, polymyositis, dermatomyositis); congenital dislocation of the hips; old polio
Vertiginous	Unsteady; falling to one side; postural imbalance; vertigo; nausea; nystagmus	BPPV; vestibular neuronitis; Ménière's disease; acoustic neuroma
Psychogenic (bizarre)	Different, dramatic verities; rare fall or injury; Hoover sign positive	Conversion disorders
Astasia-abasia (Blocq disease)	Lack of motor coordination which leaves the patient unable to stand or walk unassisted but normal leg movements can be done when in a sitting or lying down position.	Conversion disorders; rarely in children with posterior fossa tumor, e.g. medulloblastoma

in which the patient is asked to stand up from a sitting position without use of hands, walk 10 feet, turn around, walk back, and sit down, is a valid procedure to readily assess gait disorders.<sup>2,3</sup> Patients who take less than 10 seconds are usually normal, patients who

take longer than 30 seconds tend to need assistance with many mobility tasks

- Gait disorders worse in the dark are due to lesions of the posterior column, e.g. Friedreich's ataxia, pernicious anemia, MS, or tabes dorsalis
- *Romberg's test (eyes-open-eyes-closed)*: Cerebellar

ataxia can be differentiated from sensory ataxia by Romberg's test, where removal of the visual input dramatically reduces compensatory ability in sensory ataxia.

- Ask the patient to stand in one place with his feet together. If he is able to stand with his eyes open as well as eyes closed, the test is negative, i.e. normal.
- If he is able to stand with eyes open, but tends to fall with eyes closed (i.e. removing visual input), the test is positive. The cause may be posterior spinal column lesions due to tumor, vit B<sub>12</sub> deficiency, cervical spondylosis, or tabes dorsalis.
- If he is unable to stand with eyes open and feet together, it indicates severe unsteadiness, commonly involving the peripheral and central vestibular system and the cerebellum.
- *Fukuda test*: Marching in place for 50 steps; abnormal if patient deviates close to 90° or more, either to left or right. If abnormal, it reflects vestibular disorder
- *Hoover sign*: It is a maneuver aimed to separate organic from nonorganic lower limb paralysis. The physician takes a position at the foot of the supine patient and places one hand under the heel of the patient's 'weak' leg while pressing down with the other hand on the good leg. Now the patient is asked to attempt to raise the affected 'weak' leg. In organic disease, the associated movement causes the unaffected heel to press downward; in hysteria, the associated movement is absent
- The *chair test* to aid in the diagnosis of psychogenic gait disorders: In this procedure of 'chair testing' patient is asked to walk 20-30 feet forward and backward toward the examiner. The patient is then asked to sit in a swivel chair with wheels and to propel the chair forward and backward. Compared with

his walking, the psychogenic patient is found to perform well on the chair test (sitting versus standing), showing improved ability to propel a chair forward than when seated. By contrast, a normal person performs equally when walking or propelling utilizing the chair.

## RED FLAGS

- In the elderly:
  - Three "Ds" contribute to gait disorder; viz. *drugs*, *depression*, and *dementia*; these must be specifically looked for and excluded before any other intervention.
  - Acute onset gait disorder is likely to be due to acute systemic decompensation, such as MI, stroke, or sepsis; a careful systematic evaluation is indicated to exclude such catastrophic presentations.
  - It is often not advisable to attribute gait disorder to a single disease because many different conditions (e.g. degenerative joint disease, postural hypotension, and stroke) can present in similar gait abnormalities.
- In a patient with history suggestive of secondary gain and normal neurological examination, except bizarre gait, strongly favors malingering.

## SELECTIVE GLOSSARY

**Brown-Séquard syndrome**—It is associated with injury to the lateral half of the spinal cord (involving interruption of the lateral corticospinal tracts, posterior white column, and lateral spinothalamic tracts), usually as a result of penetrating trauma to the cervical or thoracic spine. Multiple causes of Brown-Séquard syndrome have been described in the literature. The most common cause remains traumatic injury, often a penetrating mechanism, such as a stab or gunshot wound or a unilateral facet fracture and

dislocation due to a motor vehicle accident or fall. The condition is characterized by the following clinical features (which are found below the level of the lesion): contralateral hemisensory anesthesia to pain and temperature, ipsilateral loss of proprioception, and ipsilateral motor paralysis. Tactile sensation is generally spared. The pure Brown-Séquard syndrome reflecting hemisection of the cord is not often observed. A clinical picture comprising fragments of the syndrome or the hemisection syndrome plus additional symptoms and signs, known as 'Brown-Séquard-plus syndrome', is more common.<sup>4</sup> In the absence of trauma, this condition needs to be differentiated from acute poliomyelitis, Guillain-Barré syndrome, cervical disk disease, vertebral artery dissection, infection and inflammatory causes. MRI is helpful to define the extent of spinal cord injury and is also helpful when differentiating among nontraumatic etiologies. CT myelography may be useful if MRI is contraindicated or not available.

**'Fear of falling' gait**—It is largely a psychogenic gait disorder of the elderly that is often unrecognized. It usually begins after a fall and is characterized by a shuffling or sliding stride and an intense need to hold on for support. It appears to be most common in elderly women, can be reversed by education, suggestion, and physical therapy, and is often mistaken for Parkinson disease, or other gait disorders in the elderly.

**Friedreich's ataxia**—FA is the most common autosomal recessive ataxia; the major pathophysiologic finding in FA is a "dying back phenomena" of axons, beginning in the periphery with ultimate loss of neurons and a secondary gliosis. Classic FA is the result of a gene mutation at the centromeric region of chromosome 9 (9q13-21.1) at the site of the gene encoding for the 210-aminoacid protein frataxin. Onset of FA is early, with gait ataxia being the usual presenting symptom. Gait ataxia manifests as progressively

slow and clumsy walking, which often begins after normal walking has developed. Diagnostic criteria of typical FA include: disease duration at least 5 years, onset < 25 age, progressive ataxia of gait and limbs, absent knee and ankle jerks, and extensor plantar responses<sup>‡</sup>. As the disease progresses, ataxia affects the trunk, legs, and arms. As the arms become grossly ataxic, both action and intention tremors may develop. Eventually, the patient is unable to walk because of the progressive weakness and ataxia, becoming wheelchair bound and ultimately bedridden. With disease progression, dysarthria and dysphagia appear, incapacitating the patient by 20, and death by 25 (40 in autosomal dominant form), especially due to cardiac failure.

**Normal pressure hydrocephalus (NPH)**—It is characterized by Adam's triad (impaired gait, urinary incontinence and dementia) — and an anatomic abnormality, i.e. enlargement of the cerebral ventricles, which can be seen on CT or MRI of brain. The gait is typically wide-based with reduced step height, stride length, and velocity, which gradually progresses to so-called 'magnetic' gait ('feet stuck to ground' — due to simultaneous contraction of opposing muscles while walking), it becomes almost impossible for the patient to initiate gait. The urinary incontinence is of 'urge' type. The precise pathogenesis of NPH is not known, but it is well-known that despite the absence of increased intracranial pressure, the drainage of CSF regularly induces transient clinical improvement, and ventriculosystemic shunting usually results in prolonged remissions. Recently, another anatomic abnormality was described in NPH—a decrease in midbrain diameter on MRI that is restored to normal by ventriculosystemic shunting. The criteria to define cerebral

<sup>‡</sup>Only diseases with decreased deep tendon reflexes and positive Babinski signs are Friedreich's ataxia, amyotrophic lateral sclerosis, B<sub>12</sub> deficiency and syphilis.

ventriculomegaly precisely are vague and difficult to establish, and enlarged ventricles are surprisingly common. Other disorders of elderly people such as Alzheimer's disease, Parkinson's disease, and cerebral atrophy may show enlarged ventricles, and demential disorders may be difficult to differentiate from each other.

**Polymyositis**—It is an idiopathic inflammatory myopathy with symmetric proximal muscle weakness, characterized by subacute or slowly progressing symmetrical weakness, primarily affecting the proximal limb and trunk muscles. The illness may occur at any age, but is most frequent in the fourth to sixth decade of life, women being more frequently affected than men. Although the initial inciting agent remains unknown, possibilities include virus-mediated muscle injury, e.g. Coxsackie virus B1, HIV, Human T-lymphotropic virus 1 (HTLV-1) Hepatitis B, influenza, echovirus, and adenovirus. Many drugs are known to cause myopathy, e.g. hydroxychloroquine, D-penicillamine, hydralazine, procainamide, phenytoin, ACE inhibitors, and statins. Patients may report muscle pain and tenderness, arthralgias or arthritis that may be confused with polymyalgia

rheumatica. Later symmetric proximal muscle weakness in the upper and lower extremities develops. Weakness of pharyngeal and laryngeal muscles, interstitial lung disease, and inflammation of the myocardium may also occur. Serum CK levels are usually elevated from 5-50 times the normal value. Other muscle enzymes — lactic dehydrogenase, aspartate aminotransferase, alanine aminotransferase, and aldolase — may be elevated. Muscle biopsy is crucial in helping diagnose PM and in excluding other rare muscle diseases. MRI can be used to guide the site of biopsy.

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## CHAPTER

# 22

## Gastrointestinal Bleeding

### SYNOPSIS

*Gastrointestinal (GI) bleeding* includes bleeding from both upper and lower GI tract.

The *upper GI* (UGI) bleeding is defined as bleeding from source above the ligament of Treitz\*, and includes the mouth, esophagus, stomach, and small intestine up to the duodenojejunal junction.

The *lower GI* (LGI) bleeding is usually defined as bleeding originating from below the ligament of Treitz, and includes the small intestine, colon, and anal canal.

The UGI bleeding manifests clinically as hematemesis and melena, and that of LGI bleeding as hematochezia.

*Hematemesis* is vomiting of blood from the UGI tract as defined above. Bright red or blood streaked vomitus indicates fresh or recent bleeding; dark red, brown, or black vomitus (the color and consistency of coffee-grounds) indicates that blood has been retained in the stomach and partially digested.

*Melena* is the passage of black, tarry stools containing altered blood; its characteristic color results from bacterial degradation, and hydrochloric acid acting on the blood as it travels through the GI tract. Thus, melena suggests that the blood has had time to be processed by the intestinal tract, implying slower bleeding that originated in the UGI tract. About 100 to 200 ml of blood in the GI tract is essential to produce melena which may persist for several days after the bleeding has ceased.

*Hematochezia* is passing *bright red blood per rectum* (BRBPR), the source of bleeding is usually from the LGI tract; however, approximately 10-15% of patients presenting with acute severe hematochezia have an UGI source of bleeding identified on upper endoscopy.

*Occult GI bleeding* (OGIB: Table 22.1) refers to chronic or intermittent loss of minute amount of blood of which the patient is unaware; i.e. there is insufficient bleeding to cause obvious melena or hematochezia. Chronic GI blood loss less than 100 ml per day may cause no apparent change in stool appearance. Therefore, OGIB in an adult is identified by positive *fecal occult blood test* (FOBT) or as a manifestation of iron deficiency anemia.

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\* An important anatomical landmark of the duodenojejunal junction which divides GI tract as UGI and LGI portion.

**Table 22.1:** Differential diagnosis of occult GI bleeding*Inflammation*

- Peptic ulcer (esophagus, stomach, duodenum, surgical anastomosis)
- Erosive esophagitis/gastritis
- Cameron lesion<sup>#</sup>
- IBD (ulcerative colitis, Crohn's disease)

*Infections*

- Hookworm/ ascariasis/ whipworm/ strongyloidosis
- Amebiasis/ giardiasis
- TB enteritis

*Neoplasms*

- Carcinoma, lymphoma, polyp

*Vascular*

- Portal hypertension
- Hemangioma
- Dieulafoy's lesion (ruptured mucosal artery: *vide infra* ↓↓)
- Watermelon stomach<sup>##</sup>
- Vascular enteric fistula

*Superstitious*

- Hemoptysis
- Oropharyngeal (epistaxis)

*Miscellaneous*

- Long distance running
- Factitious
- Hemobilia

<sup>#</sup>*Cameron lesions* are linear gastric ulcers or erosions positioned on the crests of mucosal folds at the diaphragmatic impression in patients with large hiatus hernia.

<sup>##</sup>*Watermelon stomach* is the popular name for Gastric Antral Vascular Ectasia (GAVE) in which the lining of the stomach bleeds, causing it to look like the characteristic stripes of a watermelon when viewed by endoscopy; it can occur in patients with diffuse systemic sclerosis.

*Obscure GI bleeding* (Table 22.2) refers to bleeding that persists or recurs, and for which there is no obvious source found after routine endoscopic (upper and lower) evaluation. Obscure GI bleeding, though uncommon, may be clinically evident, manifesting as recurrent melena, hematochezia, iron deficiency anemia, or positive FOBT.

GI bleeding is most commonly a result of benign pathology, which resolves spontaneously and has favorable outcomes.<sup>1</sup> However, long-term

**Table 22.2:** Differential diagnosis of obscure GI bleeding

- Aortoenteric fistula
- Dieulafoy's lesion
- Diverticula
- Extraesophageal varices (gastric, small bowel, colonic)
- Hemobilia
- Meckel's diverticulum
- Neoplasms (small bowel)
- Vascular ectasias

recurrence is a substantial problem, especially for elderly patients with LGI bleeding.<sup>2</sup> Additionally, the stability of the patient and the rate of bleeding dictate the order in which various diagnostic procedures should be conducted. Therefore, the goal is to identify, and if necessary, treat the source of bleeding, while maintaining hemodynamic stability of such patient.

## DIFFERENTIAL DIAGNOSIS

As noted above, the source of GI bleeding may be categorized into two broad groups: viz. UGI bleeding and LGI bleeding.

## A—UGI BLEEDING

### Common

- Peptic ulcer disease (PUD; *H. pylori* infection)
- Esophagitis (due to chronic GERD)
- Erosive gastritis (NSAIDs, aspirin, steroids, stress, alcohol).

### Occasional

- Esophageal varices (cirrhosis of the liver, portal hypertension)
- Mallory-Weiss tears (i.e. MW tears: *vide infra* ↓↓)
- Erosive duodenitis.

### Rare

- Cancer of esophagus
- Cancer of stomach
- Aortoduodenal (aortoenteric) fistula (primary and secondary).

- Hemobilia (blood in bile)
- Bleeding disorders (anticoagulant induced coagulopathy, thrombocytopenia)
- Iatrogenic bleeding (due to anticoagulant usage, e.g. heparin, warfarin, or thrombolytic therapy).

## B—LGI BLEEDING

### Common

- Anal disease (fissure/ulcer, hemorrhoids)
- Colitis—acute infections (bacterial, parasitic)
- Colitis—chronic infections (TB, amoebiasis, ancylostomiasis).

### Occasional

- Inflammatory bowel disease (IBD – ulcerative colitis, Crohn’s disease)
- Pseudomembranous colitis (PMC)
- Rectal varices (portal hypertension, splenic vein thrombosis)
- Polyps/postpolypectomy bleeding.

### Rare

- Colitis – ischemic, radiation
- Solitary rectal ulcer syndrome (SRUS: *vide infra* ↓↓)<sup>3,4</sup>
- Diverticulosis/pseudodiverticulosis
- Colonic neoplasm (adenocarcinoma)
- Carcinoid tumor
- HIV/AIDS colitis (Cytomegalovirus colitis, colonic histoplasmosis, Kaposi’s sarcoma of the colon, and bacterial colitis)
- Colonic arteriovenous (AV) malformation (i.e. vascular ectasias, angiomas, angiodysplasias, and Heyde’s syndrome<sup>†</sup>)
- Systemic/iatrogenic bleeding disorder
- Vasculitis (PAN, Wegener granulomatosis).

<sup>†</sup> The Heyde’s syndrome consists of the association of gastrointestinal bleeding from angiodysplasia with aortic valve stenosis.

## INVESTIGATIONS—GENERAL

### CBC

- Baseline Hb – low in chronic bleeding.
- A low hematocrit and MCV in a stable patient suggests intermittent, chronic bleeding.
- Serial estimation of hematocrit (i.e. PCV) can be useful in assessing ongoing blood loss.

### Coagulation/Clotting Screen

- PT, PPT and platelet count—to assess bleeding diathesis, liver disease, and to monitor anticoagulant therapy.
- Blood group and cross matching, if bleeding is ongoing.

### Serum Chemistry/Serology

- Blood urea is elevated disproportionately to creatinine in patients with GI bleeding (due to reabsorption of blood from the bowel).
- Electrolytes—if vomiting/diarrhea are ongoing.
- HIV serology—as indicated.

### LFTs

- AST, ALT, and Alk. Phosphatase – elevated in hepatitis, cirrhosis, and neoplasm.

### ECG

- To rule out cardiac ischemia due to hypovolemia and related factors, especially in the elderly.

### EGD

- Diagnostic procedure of choice for acute UGI bleeding; can demonstrate most lesions, e.g. varices, esophagitis, PUD, gastric erosions, MV tear, and carcinoma
- Screening procedure in patients with cirrhosis and portal hypertension, but without prior variceal hemorrhage
- Advantages of early EGD include: confirmation of bleeding source in UGI tract; obtaining

biopsy (Bx), and providing therapeutic measures which lessen transfusion requirements, need for surgery, and hospitalization.

## INVESTIGATIONS—SPECIFIC

### Sigmoidoscopy

- Useful primarily in patients < 40 years of age for minor bleeding due to low-lying anal disease.

### Colonoscopy<sup>5,6</sup>

- First procedure of choice in LGI bleeding diagnosis; may be performed urgently or electively depending on patient's hemodynamic status and risk-stratification criteria such as positive FOBT in patient > 40 years of age
- Though colonoscopy is recommended for patients with LGI bleeding, it may also be used in combination with EGD (i.e. *bidirectional endoscopy*) for patients with upper GI bleeding, OGIB, or nondiagnostic EGD
- Advantages include: direct visualization; access for tissue biopsy (Bx), and ability to treat bleeding lesions primarily with heat probe, laser therapy, band ligation, or hemoclippping.

### Angiography (Mesenteric)

- Used for active, heavy bleeding and/or if colonoscopy is inconclusive
- The main advantage include: accurate localization of bleeding sites that are not identified by endoscopy
- It may also permit therapeutic interventions, e.g. vasopressin infusion and embolization. Complications such as renal failure, rebleeding may occur.

### Multidetector Computed Tomographic (MDCT) Angiography<sup>7-9</sup>

- MDCT angiography is a promising first-line modality for fast and accurate localization of acute GI and intraperitoneal bleeding.

### <sup>99m</sup>Tc RBC Scanning

- Like angiography, it is only of value in patients with active bleeding. The newer techniques involving dynamic imaging (more frequent acquisition of data), extra large field-of-view gamma cameras, and cine scintigraphy, or movie-mode displays have proved to have an accuracy of nearly 90% in the localization of the bleeding site
- Also most often employed in confirming Meckel's diverticulum.

### Abdomen US/HRCT

- May be indicated to diagnose associated disorders such as pancreatitis, aortic aneurysm, ascites, metastasis, and aortic graft infection.

### Double-contrast Barium Enema

- May be an alternative in patients with contraindications to colonoscopy.

### Small Bowel Imaging

- When endoscopy is undiagnostic, the small bowel is evaluated. Common procedures employed are contrast radiography, i.e. UGI barium follow-through series, and push enteroscopy, which is an extension of EGD that allows visualization up to 160 cm. of small bowel distal to ligament of Treitz; allows tissue biopsy (Bx), and treatment of bleeding lesions up to 160 cm. of the proximal small bowel.

### Capsule Endoscopy<sup>10,11</sup>

- It is a noninvasive visual evaluation of the entire small bowel and esophagus, indicated in:
  - Suspected small intestinal bleeding in persons with objective evidence of recurrent, obscure gastrointestinal bleeding (e.g. iron-deficiency anemia, positive fecal occult blood test, or visible bleeding) who have had EGD and colonoscopy within the past 12 months that have failed to identify a bleeding source.

- For initial diagnosis in persons with suspected Crohn's disease without evidence of disease on conventional diagnostic tests, including small-bowel follow-through and upper and lower endoscopy.
- For screening or surveillance of Barrett's esophagus, and esophageal varices.

### Echocardiography

- There is a well-recognized association between angiodysplasia and aortic stenosis and replacement of the stenotic valve has been reported to stop GI bleed in over 90% of patients. Echocardiography should therefore be a part of the investigations in such cases.<sup>12-14</sup>

### Laparotomy with Intraoperative Enteroscopy

- A last option in the diagnostic evaluation of nonemergent cases.

### CLINICAL NOTES

- Confirm hematemesis; patients often confuse vomiting up and coughing up blood. A history of epistaxis, bleeding gum disorders, hemoptysis indicate sources other than GI tract. Ideally viewing the vomit is the best way to confirm hematemesis
- Confirm melena; black stools may result from ingestion of iron salts, charcoal, beets, etc.
- Patients with severe bleeding may present with signs of shock (tachypnea, tachycardia, hypotension; systolic blood pressure <100 mm Hg usually indicates <30% reduction in blood volume), which in patients with co-morbid disease such as IHD may precipitate angina or MI because of hypoperfusion. However, resuscitative measures and appropriate level of patient monitoring must be established before diagnostic testing or specific therapeutic interventions
- Nasogastric lavage should be performed in patients with UGI bleeding. Nasogastric lavage may be useful as a diagnostic technique. A bloody lavage may be helpful in predicting a high-risk lesion, particularly in hemodynamically stable patients without hematemesis; a clear lavage may be helpful in predicting low-risk lesions. Nasogastric lavage can also facilitate endoscopic visualization by clearing blood and other gastric contents. A negative lavage, however, does not exclude upper GI bleeding; the procedure carries a false-negative rate of 10%. The bleeding in such cases may be intermittent or located in the duodenum. Aspiration of bilious, nonbloody material strongly indicates that no active duodenal bleeding is occurring<sup>15, 16</sup>
- In UGI bleeding important historical information should include the onset, character, frequency, and quantity of hematemesis. Peptic ulcer pain is epigastric, gnawing, rhythmic, and dull. GI malignancy is associated with vague epigastric pain, dyspepsia, or weight loss. Coughing, retching, or vomiting preceding hematemesis suggest MW tears
- Although LGI bleeding is usually painless, a history of abdominal pain, weight loss, fever, diarrhea, vomiting, or partial small intestinal or colonic obstruction are important findings in the differential diagnosis of inflammatory, infectious, or malignant lesions. Diverticular disease presents as painless with high volume bleeding. Cancer and angiodysplasia present with symptoms of chronic blood loss (anemia, fatigue, dyspnea on exertion)
- History of prior GI or vascular surgery, e.g. aortic bypass, and history of any comorbid disease such as pancreatitis, cirrhosis, renal failure, cancer, etc. precipitates hematemesis

- A history of cutaneous bleeding (e.g. purpura, ecchymosis) may indicate bleeding diathesis (e.g. hemophilia, hepatic failure)
- Age is an important feature in discriminating the source of LGI bleeding. For patients aged more than 50 years, ischemia, colonic AV malformation, diverticulosis, and malignancy are most common<sup>17</sup>
- Colonic AV malformations are most commonly found in the cecum, often associated with several systemic diseases, including atherosclerotic cardiovascular disease, aortic stenosis (*Heyde's syndrome*), chronic renal disease, collagen vascular disease, von Willebrand disease, and cirrhosis of the liver
- Medications—NSAIDs, steroids, and use of recreational drugs, cigarettes, or alcohol increase the incidence of erosive gastritis or ulcer disease
- Because of increasing number of elective aortic aneurysm repairs in the aging population, it is likely that more patients with secondary aortoenteric fistula will present with LGI bleeding. Hence, a high index of suspicion is necessary for prompt diagnosis and management of this life-threatening event
- The clinical findings of initial physical examination and their possible etiologies are given in Table 22.3.

## RED FLAGS

- It is crucial to remember that identification of a benign anorectal lesion (hemorrhoids, ulcer, etc.) does not eliminate the possibility of a more proximal cause of hemorrhage. In general, patients with hemorrhoids identified by physical examination should still undergo thorough endoscopic evaluation of the colon to rule out other pathological conditions (e.g. portal hypertension, anorectal varices, etc.).

**Table 22.3:** Physical examination in GI bleeding

General or system	Etiologies
<ul style="list-style-type: none"> <li>• Weight loss; cachexia</li> <li>• Vitals—Pulse-tachycardia, – low volume; – BP—hypotension</li> <li>• Skin and mucous membrane: Erythema nodosum Jaundice Pallor; ecchymosis</li> <li>• Cutaneous telangiectasis</li> <li>• Pigmented macules on the lips</li> <li>• Nose and oral cavity</li> <li>• Neck: JVP</li> <li>• Lymph nodes</li> <li>• Cardia: Murmurs</li> <li>• Lungs: Basal rales/crepitations</li> <li>• Abdomen: Epigastric tenderness Hepatosplenomegaly; ascites Mass Bruit</li> <li>• Rectal examination:</li> <li>• Nasogastric aspirate</li> </ul>	<ul style="list-style-type: none"> <li>• Systemic disease</li> <li>• Significant blood loss</li> <li>• IBD</li> <li>• Liver disease</li> <li>• Coagulation disorder</li> <li>• Hereditary hemorrhagic telangiectasia; (Rendu-Osler-Weber: <i>vide infra</i> ↓↓)</li> <li>• Peutz-Jeghers syndrome: <i>vide infra</i> ↓↓</li> <li>• Ectopic bleeding source? present</li> <li>• Volume status</li> <li>• HIV, leukemia, metastasis</li> <li>• Angiodysplasia associated with aortic stenosis</li> <li>• Volume status</li> <li>• PUD; <i>H. pylori</i></li> <li>• Cirrhosis of the liver; malignancy</li> <li>• Crohn's disease; malignancy</li> <li>• Aortic aneurysm</li> <li>• Fissure; hemorrhoids; mass</li> <li>• Bright red or 'coffee-ground' in UGI bleeding; positive for blood</li> </ul>

- Positive FOBT may be the first sign of colon cancer or polyp, particularly in patients above 45 years of age
- Solitary rectal ulcer syndrome should be considered in all patients with malignant looking rectal tumors
- Aortoenteric fistula must be suspected in any patient presenting with UGI bleeding with known aortic graft (e.g. prior aortic aneurysm repair). Urgent diagnosis and surgery is mandatory to prevent exsanguinating hemorrhage
- Most commonly missed OGIB disorders related to UGI segment are: erosions in large hiatal hernias; AV malformations, and peptic ulcer on the first endoscopic evaluation
- The LGI lesions most commonly missed on initial endoscopy are: AV malformations and neoplasms. Repeat upper, lower, or bidirec-



tional endoscopy may be essential depending on clinical suspicion, and to ascertain that these lesions have not been overlooked.

### SELECTIVE GLOSSARY

**Dieulafoy's lesion**—It is an abnormally large artery that penetrates the gut wall, mainly in the proximal stomach, causing massive bleeding. The lesion bleeds into the GI tract through a minute defect in the mucosa, which is not a primary ulcer of the mucosa, but erosion probably caused on the submucosal surface by the pulsatile arteriole protruding into the mucosa. Dieulafoy's lesion is most commonly located in the proximal stomach (75% of cases). Lesion typically occurs within 6 to 10 cm of the esophagogastric junction, generally along the lesser curvature of the stomach. Detection and identification of the Dieulafoy's lesion as the source of bleeding can often be difficult, especially because most present with massive bleeding. Because of intermittent nature of bleeding, initial endoscopy is diagnostic in 60% of the cases, so repeated endoscopies are often necessary. Similar lesions have been identified in the duodenal bulb, jejunum, ileum, colorectum, anal canal, and even in bronchus. With the advances in endoscopy and awareness of Dieulafoy's lesion as the cause of massive bleeding that can cause a high fatality rate if the condition remains unrecognized, it has gained the reputation of an unusual but important cause of bleeding, especially LGI hemorrhage.

**Hereditary hemorrhagic telangiectasia (HHT / Rendu-Osler-Weber Syndrome)**—It is a hereditary disease of vascular malformation transmitted as an autosomal dominant trait affecting men and women, characterized by the presence of multiple arteriovenous malformations (AVMs) that lack intervening capillaries and result in direct connections between arteries and veins. Small AVMs (or telangiectases) close to the

surface of skin and to mucous membranes often rupture and bleed after slight trauma. The most common clinical manifestation is spontaneous and recurrent epistaxis beginning at approximately 12 years of age. About 25% of individuals with HHT have GI bleeding, which most commonly begins after age 40 years. Large AVMs often cause symptoms when they occur in the brain, lungs, or gastrointestinal tract, causing complications from bleeding or shunting, which may be sudden and catastrophic. The diagnosis of HHT is based on family history and the presence of cutaneous or mucocutaneous telangiectases or large visceral AVMs. HHT is caused by a mutation in *ENG*, the gene encoding endoglin or *ACVRL1 (ALK1)*, the gene encoding the activin receptor. Molecular genetic testing of these genes detects mutation in 60-80% of individuals with HHT and is available on a clinical basis.

**Mallory-Weiss syndrome**—It is characterized by UGI bleeding secondary to longitudinal mucosal lacerations at the gastroesophageal junction or gastric cardia; may occur after any event that provokes a sudden rise in intragastric pressure or gastric prolapse into the esophagus secondary to precipitating factors such as retching or vomiting. The classic presentation consists of an episode of hematemesis following a bout of retching or vomiting. Hematemesis is present in 85% of patients. Less common presenting symptoms include melena, hematochezia, syncope, and abdominal pain. Excessive alcohol use has been reported in 40-75% of patients, and aspirin use in up to 30%.

**Peutz-Jeghers syndrome**—It appears to be a germline mutation of the *STK11* gene, located on band 19p13.3.; characterized by the combination of pigmented lesions in the buccal mucosa and gastrointestinal polyps. Mucocutaneous pigmentation and melanin spots are typical, and are present in more than 95% of cases. They appear as small, flat, brown, or dark blue spots with an

appearance of freckles, most commonly in the peribuccal area. The number, as well as the size and the location of polyps may vary from patient to patient. Isolated melanotic mucocutaneous pigmentation without gastrointestinal polyps has also been described because of the genetic variability of the syndrome. Presentation may include — repeated bouts of abdominal pain in patients younger than 25 years, unexplained intestinal bleeding in a young patient, and menstrual irregularities in females. Family history of Peutz-Jeghers syndrome may be present. Many of the gastrointestinal lesions will start developing early in life even if the syndrome is clinically apparent in the second and third decades of life. (Pigmented lesions are present in the first years of life and may fade at puberty, except for those on the buccal mucosa, making diagnosis possible in pediatric patients with a high level of suspicion). Genetic counselling and proper screening for both intestinal cancers and extraintestinal cancers should be implemented.

**Solitary rectal ulcer syndrome (SRUS)**—It is a rare debilitating disorder of the rectum, characterized by perianal chronic pain with passage of blood and mucus. The macroscopic appearance varies from single to multiple ulcers or even circumferential lesions. The pathogenesis remains uncertain; however, trauma to the anterior or circular rectal wall caused by straining due to functional disorders of defecation, and pelvic floor disorders are the main hypothesis. The diagnosis includes clinical symptoms associated with endoscopic lesion (erythema, ulcer or polypoid lesion). Defecography, transrectal ultrasonography, anorectal manometry, dynamic MRI, etc. are suitable procedures that may be used to detect the causative disorder. Histopathological features of SRUS are characteristic and pathognomonic; nevertheless the endoscopic

and clinical presentations may be confusing. The lesions may mimic other rectal pathologies, including primary or metastatic malignancy, and lead to wrong diagnosis.

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## CHAPTER

# 23

## Headache

### SYNOPSIS

The term *headache* may be defined as any painful or nonpainful discomfort perceived more than momentarily in the cranial vault, the orbits, and the nape of the neck, i.e. from the orbits back to the suboccipital area\*.

It is often difficult to explain the pain of headache. Hence it is sometimes equated to ‘invisible misery’, where quite often nothing is seen from outside and nothing is measurable on the inside.<sup>1</sup> Some terms used by patients to explain their headache are—pressure, heaviness, tightness, throbbing, pounding, boring, bursting, or simply dull aching discomfort.

The diagnosis of headache nowadays is based on the classification criteria of The International Headache Society (IHS). The new International Classification of Headache Disorders (ICHD-II) published in January 2004 classifies headache disorders into 3 parts: part 1: primary headache, part 2: secondary headache, part 3: neuralgias and facial pain, and appendix. In total 14 different headache groups and more than 170 headache types are separated.<sup>2-4</sup>

\* Pain elsewhere in the face is not included.

The primary headache disorders—those *not* associated with an underlying pathology—include migraine, tension-type, and cluster headache. Secondary headache disorders—those attributed to an underlying pathologic condition—include any head pain of infectious, neoplastic, vascular, drug-induced, or idiopathic origin. The vast majority of patients who present with headache have one of the primary disorders, as serious secondary causes for presentation with head pain are rare.

However, patients suffering from headaches usually fear serious brain disease, and may in fact be the harbinger of a life-threatening illness. Further, besides the conventional CT, MRI, MRA, PET, and SPECT scans, recent imaging modalities such as *functional MRI* (f MRI) and *voxel-based morphometry* (VBM) on MRI has the potential to change our concept of primary headache disorders, requiring a radical reappraisal of the tenet of structural normality.<sup>5</sup>

In the maze of such advanced neuroimaging realities, their diagnostic outcomes, cost-effectiveness, and their constant demand for novel imaging strategies, “whether it’s nobler to scan the brain or suffer the slings and arrows of the aggrieved patient or relative, that is the clinical problem.”<sup>6,7</sup>

Therefore, the clinician's prime concern while examining headache patients is, to try and distinguish the more common benign from the less common serious life-threatening causes of headache<sup>†</sup>, while maintaining a balanced approach to diagnostic testing.

## DIFFERENTIAL DIAGNOSIS

### Common

- Systemic illness (febrile episodes: viral, typhoid, malaria)
- Migraine
- Tension headache
- Chronic daily headache
- Psychogenic (depression, anxiety)
- Vascular (subarachnoid hemorrhage, i.e. SAH; intracerebral hemorrhage)
- CNS infections (i.e. meningitis: bacterial-*Streptococcus pneumoniae*, *H. influenzae* type b, *N. meningitidis*; TB; viral – HIV, HSV2, EBV; parasitic – **toxoplasma**; fungal – **cryptococcal**<sup>‡</sup>)
- Post-traumatic headache
- Premenstrual headache
- Drug induced (nitrates; calcium channel blockers; phosphodiesterase type 5 inhibitors: sildenafil; insulin: hypoglycemia)
- Substance abuse (alcohol, caffeine, nicotine)
- Analgesic rebound headache (analgesics, NSAIDs, ergotamine)
- Cervical spondylosis
- Referred pain (sinus, dental, aural).

### Occasional

- Cluster headache
- Chronic subdural hematoma
- Accelerated/malignant hypertension
- Neoplasms (space occupying lesions, i.e. SOL)

<sup>†</sup> The list of differential diagnoses is one of the longest in all of medicine.

<sup>‡</sup> Especially in patients with immunocompromised status.

- Ocular (acute narrow angle glaucoma, refractory errors)
- Lumbar puncture headache.

### Rare

- Thunderclap headache (i.e. TCH – *vide infra* ↓↓).
- Giant cell arteritis (GCA)
- Benign intracranial hypertension
- Cerebral venous thrombosis
- Coital/sexual headache.<sup>8</sup>

## INVESTIGATIONS—GENERAL

### CBC

- Rarely useful or definitive, except in a febrile patient.

### ESR

- Elevated ESR (61-80 mm/hr) is useful to support the diagnosis of GCA.

### Skull X-ray

- Immediately after head injury; CT scan is superior.

### X-ray PNS

- Useful if sinusitis is suspected – opacification, fluid level, mucosal thickening may be visualized.

## INVESTIGATIONS—SPECIFIC

### Blood Culture

- Indicated in cases of CNS or systemic infection.

### Biochemistry

- Electrolytes, urea, creatinine, blood glucose, LFT, TFTs, and VDRL may be indicated to exclude secondary causes of headache.

**CXR/Spine X-ray**

- To rule out the possibility of metastatic carcinoma/cervical spondylosis.

**CT**

- Indicated in evaluating for PNS and diagnosing SAH or intracerebral hemorrhage in patients with acute and severe headache
- However, a normal CT scan, including fifth generation multislice detector CT scan investigations and reports does not rule out an acute bleed; if the clinical suspicion remains high, a LP should be performed
- Limitations of brain CT include inability to identify small hemorrhages in areas obscured by artifact or bone, inability to diagnose other conditions such as idiopathic intracranial hypertension, meningitis, carotid or vertebral artery dissection, and some cases of cerebral venous sinus thrombosis or pituitary apoplexy, and decay in sensitivity with time (sensitivity 92% day of rupture and 58% five days later).<sup>9</sup>

**CSF**

- CSF analysis is indicated when meningitis, encephalitis, and SAH are diagnostic consideration
- LP should not be performed when increased ICP is suspected, until mass effect is ruled out<sup>§</sup>
- The totality of the evidence suggests that lumbar puncture must still be performed after a negative CT scan result in patients being evaluated for subarachnoid hemorrhage.<sup>10</sup>

<sup>§</sup> Because a lumbar puncture can precipitate brain herniation and death in the presence of increased intracranial pressure, a CT scan is warranted before the lumbar puncture is performed.

- The sensitivity of lumbar puncture approaches 100% one to five days after the hemorrhage when photospectrometry is used to detect xanthochromia in the fluid sample.

**MRI**

- It is useful in further enhancing lesions detected by CT, especially in patients with chronic headache
- MRI is superior in detecting posterior fossa tumors and to demonstrate small aneurysms
- In patients with atypical or complicated headache patterns, e.g. a history of seizures and/or focal neurological signs or symptoms, MRI is the preferred choice
- MRI is the modality of choice in the diagnosis of headaches in patients with HIV/AIDS, who have a wide variety of neuroimaging abnormalities, and also coexistence of multiple pathologies, e.g. tuberculoma with cerebral infarcts.

**Temporal Artery Biopsy**

- Giant cells may be seen in temporal arteritis. However, a normal biopsy does not exclude the disease as there may be segmental involvement of the temporal artery.

**PET/SPECT Imaging**

- Nuclear medicine examinations of the cerebral circulation and metabolism can be carried out in subgroups of headache patients for diagnosis and evaluation of complications, when patients experience unusually severe attacks, or when the quality or severity of attacks has changed.<sup>11</sup>

**MR Angiography (MRA)**

- Useful to demonstrate small aneurysms.



**IOP**

- In patients with glaucoma, tonometry will show high intraocular pressure.

**CLINICAL NOTES**

- Five questions need to be answered when dealing with a patient with headache:
  1. Is it the only symptom (e.g. tension headache); or associated with other symptoms (e.g. visual aura in migraine, neurological deficit in stroke)?
  2. Is it an acute, new-onset symptom (e.g. CVD, temporal arteritis)?
  3. Is it a chronic, recurring symptom (e.g. migraine, substance use or abuse)?
  4. Is it part of the systemic illness (e.g. SOL, depression)?
  5. Does it represent a potentially serious threat to life (e.g. stroke, temporal arteritis)?
- In clinical practice, one useful guide in determining the cause of headache is the time course, which can be usually separated into acute, subacute, and chronic (Table 23.1). Generally, patients with acute or subacute headaches are more likely to have significant pathology
- Since most patients with *primary* headache have very little by way of physical findings, a good history is often the most important part of the headache consultation. A carefully taken history can establish the diagnosis of migraine, cluster, or tension-type headache with sufficient confidence that no need will exist for additional evaluation<sup>12</sup> (Table 23.2)
- The most common type of headache in patients presenting for consultation is the non-migrainous vascular headache secondary to systemic infection. These patients typically are febrile and have symptoms of systemic illness. The neurological examination is normal and there is no neck rigidity.

**Table 23.1:** Headache classified on the basis of time course*Hyperacute (onset within seconds to minutes)*

- Subarachnoid hemorrhage
- Intracerebral hemorrhage
- Hypertensive crisis
- Thunderclap headache

*Acute (onset within minutes to hours)*

- Intracerebral hemorrhage
- Venous sinus thrombosis
- Rapid increase in ICP (e.g. intraocular bleeding, vitreous hemorrhage)
- Occlusive hydrocephalus (intraventricular hemorrhage, cerebellar infarction)
- Migraine
- Cluster headache
- Meningitis, encephalitis
- Drugs (e.g. vasodilators, hypoglycemia)
- Acute glaucoma
- Alcohol-hangover

*Subacute (onset within days to weeks)*

- Raised ICP
  - Abscess
  - Tumor
  - Subdural hematoma
  - Hydrocephalus
  - Benign intracranial hypertension
- Temporal arteritis
- Referred (sinuses, teeth, ears, jaws, cervical spine)

*Chronic (lasting over months)*

- Continuous:
  - Tension headache
  - Psychological – anxiety, depression, hypochondriasis
  - Post-traumatic
  - Referred (as above)
- Intermittent
  - Migraine

- History of trauma may cause concussion and postconcussion headaches; intracranial SOL (Table 23.3), and cervical sprain, can also induce headaches
- History of substance abuse indicates the possibility of ‘hangover’ headache
- History of bilateral, nonthrobbing headache that is worse in the morning, may awaken the patient at night, is typical of increased ICP. Immediate neuroimaging is necessary to ascertain the cause

**Table 23.2:** Comparison of clinical features of primary headaches

	<i>Migraine</i>	<i>Tension headache</i>	<i>Cluster headache</i>
Symptoms	Photophobia; phonophobia; GI upset (e.g. anorexia, nausea, vomiting); 'aura' with brain dysfunction (e.g. headache, vertigo, dysarthria)	Disturbed memory or concentration; labile moods-irritability, restlessness; sleep disturbance; fatigue	Parasympathetic overactivity: all ipsilateral - lacrimation; red conjunctiva; scleral injection; nasal congestion/rhinorrhea; ptosis; miosis of the eye; forehead and facial sweating
Location/character	Typically unilateral; intense pulsatile, pounding, throbbing, and/or debilitating	Bilateral, all over the head; weight-like or vise-like pressure; nonpulsatile; distracting, but not debilitating	Always unilateral orbital, supraorbital, and/or temporal; severe excruciating stabbing or burning pain
Frequency/duration	Intermittent; 4-72 hours	Daily or near daily; 30 min-few days; may be constant	From 1 every day to 8 per day; remission for few months or even years; 15 min-2 hours
Triggers	Stressful event; food (chocolate, red wine); skipping meals; changes in sleep/weather; hormone fluctuations	Anxiety, stress, lack of sleep	Alcohol; selected drugs like histamine or nitroglycerin

**Table 23.3:** Headache features suggestive of a space occupying lesion

- New onset in adult life (>40 yr of age) or significant change in established pattern
- Progressive in nature
- Association with any of the following:
  - Nausea or vomiting not explained by migraine or systemic illness
  - Nocturnal occurrence or morning awakening
  - Precipitation or worsening by changes in posture, Valsalva maneuver
  - Confusion, seizures, or weakness in extremities

- Typical physical findings that may be noted in *secondary* or *symptomatic* headache are listed in Table 23.4
- The presence of nuchal rigidity should make one think of a subarachnoid hemorrhage, cerebral hemorrhage, meningitis, or cerebral abscess
- An acute onset of a headache can be a serious problem. It should be taken seriously because an abrupt onset of a severe (worst headache ever experienced) occipital or generalized headache in a patient with no past history of headache may mean a subarachnoid hemorrhage or meningitis

**Table 23.4:** Typical findings in symptomatic/secondary headache

- Pressure pain/tenderness (sinus, temple)
- Pathologic murmurs (neck, orbits)
- Meningism (i.e. clouding of consciousness, vomiting)
- Meningitis (i.e. altered consciousness, neck stiffness, fever, photophobia, etc.)
- Cranial nerve palsy and other local motor/sensory deficits
- Horner's syndrome (triad of miosis, i.e. constricted pupil; partial ptosis; and loss of hemifacial sweating, i.e. anhidrosis)
- Papilledema/retinal hemorrhage

- An acute headache with papilledema and focal neurologic signs, one should consider cerebrovascular accident/hemorrhage, cerebral abscess. With a chronic headache and papilledema or focal neurologic signs, one should consider a SOL such as a primary brain tumor or metastatic neoplasm
- Headache that is always on the same side, associated with seizures, visual disturbances, focal neurological deficit, and audible cranial bruit strongly indicates an arteriovenous malformation

- The presence of a tender superficial temporal artery should make one think of GCA (temporal arteritis), particularly in the elderly
- Cranial nerve palsies in the elderly are usually due to ischemia, but when they occur in conjunction with an elevated ESR and headache, they could be associated with GCA. However, when assessing an older person with a headache, the information obtained from the patient should be considered as carefully as any ESR result
- In *complicated* migraine such as ophthalmic / hemiplegic/basilar artery migraine, significant neurologic complications may outlast the headache phase. Very rarely there may be permanent neurologic deficit
- A patient known to have migraine can develop severe headache due to other intracranial conditions, and hence if there is any question about the diagnosis, further neuroimaging may be necessary
- If headaches are chronic and episodic, and there are no focal neurologic signs, papilledema, or nuchal rigidity, an imaging study can be postponed for a while until the response to treatment is evaluated. However, if the response to treatment is poor, neuroimaging is indicated (Table 23.5)
- Establishing an open and honest physician-patient relationship is essential for the proper evaluation and management of headache disorders.<sup>13</sup> The reason for brain scan – CT or MRI – particularly with primary headache, and its probability in the diagnosis should be made clear to the patient. Failing to provide such explanation could cause anxiety in a patient, especially when the scans are either reported as normal or incidental (nonpathologic) findings are noticed<sup>14</sup>
- Often, the most important therapeutic intervention is confident reassurance about the absence of serious underlying neurologic disease.

**Table 23.5:** Which patients with headache require neuroimaging?

- |  |
|--|
| <ul style="list-style-type: none"> <li>• Patients with older age (over 50-60 years old) with new headache</li> <li>• Occipital location of pain</li> <li>• Worsening headache with valsalva</li> <li>• Headache waking patient from sleep</li> <li>• Headache associated with syncope, nausea, or sensory distortion</li> <li>• Sudden onset severe headache (reaching maximum intensity over seconds to a minute)</li> <li>• HIV/AIDS patients with new or different headache</li> <li>• Pregnant patients</li> <li>• Abnormal finding on neurologic examination</li> </ul> |
|--|

Source: The American College of Emergency Physicians (ACEP) June 2008, Guidelines for evaluation of patients with acute headache.

## RED FLAGS

- Any headache associated with systemic symptoms or illness (including fever, persistent or progressive vomiting, stiff neck, pregnancy, malignancy, immunocompromised state, and anticoagulant therapy)
- Onset of new or sudden headache in an elderly (especially in those age 40 years or older) has to be evaluated with caution because it could herald a serious problem such as SOL, temporal arteritis, or vertebro-basilar insufficiency
- Any headache with neurologic signs or symptoms (including altered mental status, focal neurologic symptoms or signs, seizures, or papilledema)
- Prior headache history that is different (e.g. headaches now are of different pattern or are rapidly progressive in severity or frequency)
- A negative temporal artery biopsy should not delay treatment when clinical suspicion is strong
- Benign coital headache—Unless a clear history of benign recurrent events can be obtained, the presentation of severe thunderclap headache during intercourse may require a full diagnostic assessment to

rule out *coital emergencies*<sup>15</sup> such as a subarachnoid hemorrhage.

## SELECTIVE GLOSSARY

**Thunderclap headache (TCH)**—As the name suggests (a single loud sound of thunder) TCHs are hyperacute, severe headaches—like a boom of thunder, becoming severe in intensity within seconds to a minute of onset and usually fade over several hours. Some of these headaches, however, can last for more than a week. Clues in history and physical examination can point to a possible serious underlying cause of TCH, such as subarachnoid hemorrhage, intracranial hematoma, cerebral venous sinus thrombosis, cervical artery dissection, ischemic stroke, pituitary apoplexy, acute arterial hypertension, spontaneous intracranial hypotension, third ventricle colloid cyst, and intracranial infections. Patients with TCH, who have evidence of reversible, segmental, cerebral vasoconstriction of circle of Willis arteries, and normal or near-normal cerebrospinal fluid evaluation are considered to have *reversible cerebral vasoconstriction syndrome (RCVS)*<sup>\*\*</sup>. Primary TCH is diagnosed when no underlying etiology is identified. In accordance with the increased utilization of cerebral imaging and availability of noninvasive techniques to image the cerebral vasculature, and interest in identifying causes of thunderclap headaches, the list of potential causes is growing rapidly. Although uncommon, patients with thunder-clap headache are to be evaluated in an emergent fashion as many of the underlying causes are associated with a serious underlying brain disorder.<sup>16, 17</sup>

<sup>\*\*</sup>Reversible cerebral vasoconstriction syndromes (RCVS) comprise a group of diverse conditions, all characterized by reversible multifocal narrowing of the cerebral arteries heralded by sudden (thunderclap), severe headaches with or without associated neurologic deficits.

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## CHAPTER

# 24

## Hearing Loss

### SYNOPSIS

*Hearing loss*<sup>\*</sup> is the subjective complaint of total or partial inability to hear sound in either one or both ears. It can occur at any age; sudden or gradual in onset; its severity may vary from mild to severe to profound; and can be reversible, temporary, or permanent, and make verbal communication difficult.

The intensity of sound is measured with the 'decibel', i.e. dB—a logarithmic unit (and not in percentage linear scale)—whose reference unit is 0 on the audiogram. Generally, normal hearing is from 0 to 20 dB, about the loudness of a soft whisper. The thresholds in the 20 to 40dB region constitute a mild hearing loss (e.g. with trouble hearing ordinary conversation); 40 to 60 dB region constitute a moderate hearing loss (e.g. where voice must be raised to be heard); and thresholds greater than 60 dB are considered severe hearing loss (e.g. where people must shout to be heard).

The term '*deafness*' is used strictly when there is little or no hearing at all. According to the

World Health Organization, the term "*deaf*"<sup>†</sup> should only be applied to individuals with hearing impairment so severe that they cannot benefit from sound amplification or hearing aid assistance; their sense of hearing is non-functional for ordinary purposes of life. The cases included in this category will be those having hearing loss more than 80dB (i.e. profound impairment) in the better ear, or total loss of hearing in both ears.

WHO grades of hearing impairment<sup>1</sup> on the basis of *pure tone audiogram* is listed in the Table 24.1.

Hearing loss can be classified as conductive, sensorineural, (Table 24.2) or both (mixed loss). *Conductive hearing loss* (CHL) occurs secondary to lesions in the external auditory canal, tympanic membrane, or middle ear. These lesions prevent sound from being effectively conducted to the inner ear. *Sensorineural hearing loss* (SNHL) is caused by lesions of either the inner ear (sensory - due to deterioration of the cochlea) or the auditory nerve (neural - lesions of the eighth cranial nerve).

<sup>\*</sup>*Hearing loss* is deterioration in hearing. *Deafness* is profound hearing loss.

The term *impaired* hearing generally describes a wide range of hearing losses, except deafness, and denotes *disability* that is commonly called as *handicap* by the society.

<sup>†</sup>The distinction between the terms "*deaf*", "*Deaf*", "*deafened*", and "*hard of hearing*" are based principally on the individual's preferred language (spoken or sign) rather than on the actual degree of hearing loss.



**Table 24.1:** WHO grades of hearing impairment

Grade of impairment	Audiometric ISO value (average of 500, 1000, to 2000, 4000 Hz)	Impairment description
0 (no impairment)	25 dBHL or less (better ear)	No or very slight problems. Able to hear whispers
1 (slight impairment)	26-40 dBHL or less (better ear)	Able to hear and repeat words spoken in normal voice at 1 meter
2 (moderate impairment)	41-60 dBHL or less (better ear)	Able to hear and repeat words using raised voice at 1 meter
3 (severe impairment)	61-80 dBHL or less (better ear)	Able to hear some words when shouted into better ear
4 (profound impairment including deafness)	81 dBHL or greater (better ear)	Unable to hear and understand even a shouted voice

This distinction is important, because sensory hearing loss is sometimes reversible and seldom life-threatening. A neural hearing loss is rarely recoverable and may be due to a potentially life-threatening brain tumor—commonly a cerebellopontine angle tumor. *Mixed hearing loss* (MHL) may be caused by severe head injury, with or without fracture of the skull or temporal bone, by chronic infection, or by one of many genetic disorders. It may also occur when a transient conductive hearing loss, commonly from otitis media, is superimposed on a sensorineural hearing loss.

Other common symptoms which may be associated with hearing loss include headache, otalgia, otorrhea, tinnitus, vertigo, development of weakness or asymmetry of the face, and an abnormal sense of taste.

The significance of hearing loss and its impact on the health and productivity of those affected by it often go unrecognized. Although loss of vision is readily acknowledged and vigorously treated, loss of hearing is often denied, minimized, or ignored.<sup>2</sup> Since either ignored or undiagnosed hearing loss—both in the young and the old—besides causing physical disability, can also lead to multiple consequences, including social isolation and depression, it is vital that early diagnosis is made, particularly of reversible causes, in addressing these issues.

## DIFFERENTIAL DIAGNOSIS

### Common

- Cerumen impaction
- Foreign body
- Otitis externa (secondary to obstruction), furuncle
- Otitis media with effusion (secretory)
- Eustachian tube dysfunction
- Tympanic membrane perforation/retraction

**Table 24.2:** Common etiologies of hearing loss

Conductive	Sensorineural	
	Cochlear (sensory) type	Retrocochlear (neural) type
<ul style="list-style-type: none"> <li>• Cerumen impaction</li> <li>• Foreign body</li> <li>• Otitis externa/media</li> <li>• Eustachian tube dysfunction</li> <li>• Tympanic membrane perforation</li> <li>• Tympanic membrane retraction</li> <li>• Cholesteatoma</li> <li>• Otosclerosis</li> <li>• Middle ear tumors—Benign/malignant</li> <li>• Trauma</li> <li>• Congenital—external ear/canal malformation</li> </ul>	<ul style="list-style-type: none"> <li>• Presbycusis</li> <li>• Noise-induced</li> <li>• Ototoxic drugs</li> <li>• Ménière's disease</li> <li>• Neurosyphilis</li> <li>• Multiple sclerosis</li> <li>• Genetic, e.g. Alport's syndrome</li> <li>• Sudden idiopathic hearing loss</li> <li>• Trauma</li> </ul>	<ul style="list-style-type: none"> <li>• Acoustic neuroma</li> <li>• Other CP angle tumors</li> <li>• Herpes zoster</li> <li>• Cerebrovascular events</li> </ul>

- Presbycusis
- Labyrinthitis—viral, bacterial
- Noise induced hearing loss (NIHL).<sup>3, 4</sup>

#### Occasional

- Ménière's syndrome
- Otosclerosis
- Barotrauma
- Ototoxic drugs (aspirin, loop diuretics, aminoglycosides, phosphodiesterase-5 inhibitors, and chemotherapeutic agents)
- Systemic disease (diabetes mellitus, hypothyroidism, meningitis, syphilis).

#### Rare

- Acoustic neuroma
- Cholestatoma
- Ear trauma, head injury
- Systemic disease (multiple sclerosis, autoimmune disorders)
- Sickle cell disease
- Genetic (autosomal dominant and autosomal recessive)
- Psychogenic (pseudohyperacusis).

### INVESTIGATIONS—GENERAL

#### CBC

- Leukocytosis in bacterial ear and labyrinth infection
- Sickle cells may be seen on peripheral blood smears.

#### ESR

- Elevated with inflammation and autoimmune hearing loss.

#### Blood Glucose

- Recurrent otitis externa raises suspicion of diabetes mellitus and warrants blood glucose monitoring.

#### Serology for Syphilis

- SNHL is caused by both congenital and acquired syphilis.

#### TFTs

- Hypothyroidism and hyperthyroidism are causes of SNHL.

### INVESTIGATIONS—SPECIFIC

#### Pure Tone Audiometry

- Useful test for discriminating the cause of hearing loss. It measures the threshold levels (i.e. the intensity at which the patient is able to perceive sound correctly 50% of the times) by presenting pure tones (i.e. electronically generated sounds of specific frequencies), the intensity of which can be increased or decreased in 5dB steps. Air conduction and bone conduction thresholds for preset frequencies for both the ears are assessed and charted in the form of a graph called audiogram. The threshold for bone conduction is a measure of cochlear function. The difference in the thresholds of air and bone conduction (A-B gap) is a measure of degree of conductive deafness. The normal threshold is considered 0 dB hearing level (HL); hearing loss is considered present if the patient's threshold is >25 dB HL. When hearing loss is such as to require loud test tones, intense tones presented to one ear may be heard in the other ear. In such cases, a masking sound, usually narrow band noise, is presented to the nontest ear to isolate it.

#### Speech Audiometry

- In this test the patient's ability to hear and understand speech is measured. Here phonetically balanced words (single syllable words, e.g. pin, thin, day, bus) and words with two equally accented syllables (spondees), such as railroad, staircase, and baseball are delivered at 30 or 40 dB above the patient's speech reception threshold (SRT) and the percentage of words correctly heard by the patient is his discrimination score (DS).

- A person with normal hearing or conductive deafness will hear 95-100% of the words correctly. DS falls markedly in sensorineural deafness, particularly of the neural type. Poor DS (below 85%) will affect the ability to understand speech, which is more marked in the presence of noise.

### **Tympanometry**

- Measures the compliance of the tympanic membrane to ambient air pressure, and does not require patient participation. A probe containing a sound source, microphone, and air pressure regulator is placed snugly with an airtight seal into the ear canal. The probe microphone records the reflected sound from the tympanic membrane while pressure in the canal is varied. Normally, maximal compliance of the middle ear occurs when the pressure in the ear canal equals atmospheric pressure. Abnormal compliance patterns suggest specific anatomic disruptions, e.g. reduced compliance at ambient pressure is seen in otosclerosis or malleus fixation; increased compliance at ambient pressure is seen in ossicular discontinuity. In eustachian tube obstruction and middle ear effusion, maximal compliance occurs with a negative pressure in the ear canal.

### **CT Scan of the Temporal Bones (without Contrast)**

- A CT scan is used to examine bony detail in patients with suspected malformation of the external auditory canal, middle ear, or inner ear, and to delineate bone erosion secondary to infection, cholesteatoma, or tumor.

### **MRI of the Head (Gadolinium-enhanced)**

- To detect lesions of the cerebellopontine angle, MRI of the head and internal auditory canal may be needed in cases of unexplained, unilateral SNHL that is associated with a

disparity in speech discrimination between ears, abnormal neurologic examination, or a combination of such symptoms.

### **Brainstem Auditory Evoked Responses (BAERs)**

- BAERs are tested by placing electrodes on the scalp overlying the auditory cortex and measuring the conduction of sound from the cochlea to the brain using a probe placed in the ear canal. A slowing in conduction between ears may indicate retrocochlear pathology, such as an acoustic neuroma. It has decreased sensitivity in the detection of small acoustic tumors when compared to MRI scanning. The main indication for this test is in evaluating asymmetric or unilateral SNHL when MRI is medically contraindicated or not tolerated by a claustrophobic patient.

### **Electrocochleography**

- Measures the earliest evoked potentials generated in the cochlea and the auditory nerve with an electrode placed on or through the eardrum. It can be used to assess and monitor patients with Ménière's disease.

### **CLINICAL NOTES**

- It is important that a proactive approach is adopted during consultation to detect hearing loss initially because the number of people—especially the elderly—who seek help for hearing symptoms is only a fraction of those affected. Few patients may complain of decreased hearing or abnormal hearing; on many occasions it is the family member or the caregiver who initiates the assessment for hearing loss
- During consultation, eliciting history, or counseling, it is important to remember that individuals with hearing disability have

diverse degree of hearing loss, and their communication may be unintelligible. Patience, understanding, and conversing slowly and clearly (do not follow the natural instinct to shout) in patient's first language are extremely important in establishing meaningful communication

- Screening in adults can be successfully carried out using the questionnaire from the Hearing Handicap Inventory for the Elderly Screening (i.e. HHIE-S) Version (Table 24.3).<sup>5-7</sup>

**Table 24.3:** Hearing handicap inventory for the elderly—screening (HHIE-S) version-questionnaire

In this test, the patient is asked the following questions:	
1.	Does a hearing problem cause you to feel embarrassed when you meet people?
2.	Does a hearing problem cause you to feel frustrated when talking to a family member?
3.	Do you have difficulty hearing when someone whispers?
4.	Do you feel handicapped by a hearing problem?
5.	Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?
6.	Does a hearing problem cause you to attend religious services less often than you would like?
7.	Does a hearing problem cause you to have arguments with family members?
8.	Does a hearing problem cause you difficulty when listening to television or radio?
9.	Do you feel that any difficulty with your hearing hampers your personal or social life?
10.	Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?
The patient responds to each question with "no" (0 points), "sometimes" (2 points), or "yes" (4 points). Interpretation of Total Scores: 0-8 = no handicap; 10-24 = mild to moderate handicap; 26-40 = severe handicap. Scores >10 suggest significant hearing impairment and necessitate follow-up.	

- *History*—Onset - *age of onset* helps to differentiate congenital and acquired causes of hearing loss, e.g. unilateral hearing loss since birth is most likely congenital, whereas adult onset unilateral hearing loss should raise suspicion of a tumor. *Sudden onset* may due to viral infection, perilymphatic fistula, barotrauma, stroke, or hemorrhage. A *gradual onset* is suggestive of

causes such as presbycusis, noise trauma, ototoxicity, tumor, or autoimmune disorders. Some forms may be intermittent, e.g. Ménière's syndrome. *Unilateral* hearing loss is most often associated with conductive causes, Ménière's disease, trauma and acoustic neuroma. *Bilateral* hearing loss is common with presbycusis, ototoxic drugs, noise trauma, and autoimmune disorders. History of fever, ear discharge, pain is associated with ear infection

- *Associated neurological symptoms*—Tinnitus is common with Ménière's syndrome; vertigo is associated with labyrinthitis. Focal neurologic deficit suggest CNS tumor or vascular insufficiency, whereas fluctuating neurologic deficit may suggest multiple sclerosis
- *Work history*—Factory workers, pilots, firefighters, engine drivers, and those exposed to chronic, recurrent loud sound are prone to hearing loss, especially without the use of protective equipment
- Current and past medications should be reviewed. Aspirin, loop diuretics, aminoglycosides, chemotherapeutic agents, etc. are known to be ototoxic. FDA has received reports of cases of sudden decreases or loss of hearing following the use of PDE-5 inhibitors (sildenafil, tadalafil, and vardenafil) for the treatment of erectile dysfunction and for the treatment of pulmonary arterial hypertension<sup>8</sup>
- Family history—May be positive in presbycusis, Ménière's syndrome, otosclerosis, and acoustic neuroma
- *Physical examination*—Evaluation of the external ear to detect obvious causes of CHL, e.g. congenital malformations, atresia, obstruction, infection, and tympanic membrane for perforation, otitis media, and cholesteatoma. A pneumatic bulb (pneumoscapy) is required

to accurately assess the tympanic membrane and the aeration in the middle ear

- **Cranial nerve testing**—Particular attention should be paid to facial nerve function, because cranial nerves VII and VIII are closely associated at the brainstem and in the temporal bone. Unilateral V, VII and VIII involvement suggests a cerebropontine angle lesion (usually a tumor). The trigeminal (V) and lower cranial nerves (IX through XII) can also be affected by a lesion at the brainstem, such as acoustic neuroma presenting as hearing loss
- Basic tests of hearing—Auditory acuity can be assessed very crudely as follows:
  1. Stand behind the patient, 3 feet away, i.e. about an arm's length and request him to close his eyes. (It is important that he cannot see your face as many deaf patients can lip read).
  2. You need to mask the nontest ear, say by inserting your finger into it.
  3. Whisper a few words at random from behind the test ear, (e.g. 31, 45, 17, 64, etc).
  4. The patient should be able to repeat these back accurately.
  5. Then perform the same test for the other ear to get a rough measure of their hearing. You could report this as (for example) "*able to hear a quiet whisper (i.e. 0-20dB) at arms length on the right ear, but only able to hear a loud conversational voice (i.e. 40-60dB) at arms length on the left*".
- Alternately, place your fingers approximately 5 cm from one ear and rub them together. The patient should be able to hear the sound generated. Repeat for the other ear. However, hearing levels are objectively and accurately assessed by pure tone audiometry
- Tuning fork tests—To assess air conduction (AC) and bone conduction (BC). Rinne's test

and Weber's test are performed to differentiate between CHL and SNHL. Table 24.2 illustrates common causes of CHL and SNHL

- The characteristics of CHL are:
  1. Negative Rinne test, i.e.  $BC > AC$
  2. Weber's lateralized (i.e. sound will be heard better) to worst ear
  3. Normal absolute bone conduction
  4. Speech discrimination is good
- The characteristics of SNHL are:
  1. A positive Rinne test, i.e.  $AC > BC$  (normal pattern will be retained)
  2. Weber lateralized to better ear
  3. Reduced absolute bone conduction
  4. Speech discrimination is poor.

### RED FLAGS

- Earwax impaction should never be missed, but it is common<sup>9, 10</sup>
- Otitis media in the adult is uncommon; such presentation in an elderly should be referred for further evaluation to rule out an underlying obstructive lesion of the eustachian tube, e.g. nasopharyngeal carcinoma
- Suspicion of cholesteatoma warrants surgical consultation
- If patient is elderly and diabetic, be suspicious of malignant otitis externa
- Patients who present with sudden SNHL should have a CT/MRI scan to exclude vascular ischemic event, acoustic neuroma, multiple sclerosis, perilymph fistula, and other CNS disorders
- In elderly people, physical examination and investigations should be focused to search for alarming symptoms, which may suggest the cause of hearing impairment is something other than age-related presbycusis
- An individual's confused behavior, poor job performance, social isolation, depression, etc. may be atypical presentation of hearing loss



**Table 24.4:** Some signs of hearing impairment in infants and young children

Parents should be alert to any signs of hearing impairment and discuss them with their child's health care provider. Some signs include:

- Failure to startle at loud sounds
- Not turning toward the sound of a voice or imitating sounds after about 6 months of age
- Lack of babbling at 9 months of age
- Not using single words by 18 months of age
- Using gestures instead of words to express needs

Parents should be concerned about hearing impairment in older children if they:

- Develop vocabulary more slowly than their peers
- Have speech that is difficult to understand or that is too loud or too soft
- Often ask for words to be repeated
- Turn on the TV too loud
- Appear inattentive at school and have difficulties learning to read or perform simple mathematics

**Table 24.5:** Normal hearing in the very young child\*

Age	Expected response
3 months	Startles to a nearby loud sound, stirs or awakens from sleep when someone talks or makes a sound, is soothed by mother's voice
6 months	Looks toward an interesting sound, turns when name is called, makes "moo," "ma," "da," "di" sounds to toys, and "coos" when listening to music
10 months	Makes own sounds, imitates some sounds, understands "no" and "bye-bye"
18 months	Understands many single words or commands, babbles in sentence-like patterns

\*Children who do not pass these minimal performance standards or whose parents suspect there is a hearing loss at any age should be referred for testing.

- Early identification of infants and children who are at risk of congenital or acquired hearing loss, and arranging for their timely referral is extremely important. (Tables 24.4 and 24.5).<sup>11</sup>

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## CHAPTER

# 25

## Hematuria

### SYNOPSIS

Blood in the urine, i.e. presence of red blood cells (RBCs) in the urine is called *hematuria*. A person with hematuria may complain of voiding high colored or altered urine color; it may be described as yellow, orange, brown, brownish-black, greenish, or frankly red. These observations must be given their due clinical significance.<sup>1</sup> As Dr. Michael Farber, Director of the Executive Health Program at Hackensack, University Medical Center in Hackensack, NJ, states, "The appearance and smell of your urine—as well as the frequency with which you have to go—can provide many clues to what else is going on in your body.....a trip to the toilet may be more revealing than you think".<sup>2,3</sup>

A normal healthy adult at his normal activity excretes up to 2 million RBCs per day, which corresponds to 1 to 3 RBCs per high power field (HPF) on microscopic examination of urine specimen\*; anything more than this is considered to be abnormal hematuria.

\* The efficacy of hematuria screening using the dipstick method to identify patients with significant urologic disease is controversial. The dipstick results should be confirmed with a microscopic examination of the centrifuged urinary sediment.

Hematuria can be classified as gross or microscopic depending on whether or not blood is visible to the naked eye.

*Gross (macroscopic) hematuria*, i.e. urine visibly red with intact RBCs on microscopic examination can result from as little as 1 ml of blood in a liter of urine; therefore, the color does not reflect the quantity of blood loss. Besides, urine color changes can be affected by a variety of drugs, foods, and endogenous resources; the resultant abnormal urine coloration has been termed as *pseudohematuria*.

*Microscopic hematuria* is defined as three or more RBCs/HPF on microscopic examination from two of three freshly voided, clean catch, midstream urine samples. Confirmation on repeat testing is indicated to account for some degree of hematuria noticed in normal healthy persons, as well as the intermittent nature of hematuria that is found in some urological diseases.

*Physiological or benign hematuria* is common and can result from menstruation, febrile episode, vigorous exercise, and bleeding from ejaculation. However, patient should undergo repeat urinalysis, i.e. sequential urine microscopy, 48 to 72 hours after cessation of such activity. No additional evaluation is necessary if the hematuria is resolved. Patients with persistent hematuria require evaluation.

*Isolated hematuria* denotes hematuria without proteinuria or casts. Although such patients may have structural glomerular abnormalities, they appear to have low risk for progressive renal disease. Nevertheless, these patients should be followed up for the development of proteinuria, hypertension, and renal insufficiency.<sup>4</sup>

*Asymptomatic microscopic hematuria* is without features of significant renal disease (no proteinuria, normal renal function, and no hypertension), and malignancy has been excluded. Although no major organization currently recommends screening for microscopic hematuria in asymptomatic adults, risk factors for significant disease should be taken into consideration, and such high risk patients should be considered for full urological evaluation after one properly performed urinalysis documenting the presence of at least 3 RBCs/HPF.<sup>5-7</sup>

Hematuria may originate anywhere in the urinary tract, i.e. kidney, ureter, bladder, prostate gland, or urethra. At times it may reflect a generalized disorder of the clotting mechanism. However, the overall objective in dealing with hematuria is to differentiate minor incidental findings that do not require treatment to highly significant lesions that are potentially serious by considering risk factors, comorbid conditions, complications of procedures, and cost-effective outcomes.

## DIFFERENTIAL DIAGNOSIS

### Common

- Urinary tract infections (UTI: cystitis, urethritis, pyelonephritis)
- Renal calculi
- Prostate (BPH, prostatitis)
- Sexually transmitted diseases
- Nephropathy (diabetic, hypertensive, drug induced).

### Occasional

- Intrinsic renal disease (poststreptococcal glomerulonephritis, nephritis, renal TB)
- Drug induced (aspirin, antiplatelets, and anticoagulants)
- Infections (infective endocarditis, malaria, HIV).

### Rare

- Malignancy (renal cell carcinoma, bladder/prostate cancer)
- Bleeding diathesis (coagulopathy, platelet dysfunction)
- Hemoglobinopathies (sickle-cell disease)
- Hereditary (Polycystic kidney disease; Hereditary nephritis, i.e. Alport's syndrome : *vide infra* ↓↓; IgA nephropathy, i.e. Berger's syndrome: *vide infra* ↓↓; Thin basement membrane nephropathy: *vide infra* ↓↓)
- Schistosomiasis (genitourinary)
- Metabolic (hypercalcemia, hyperuricosuria)
- Vasculitis
- Foreign body trauma.

## INVESTIGATIONS—GENERAL

### CBC

- Hb% reduced due to gross hematuria, malignancy, blood dyscrasias, and CRF
- Hb% elevated due to polycythemia associated with hypernephroma
- Leukocytosis in infection, inflammation
- Thrombocytopenia in blood dyscrasias
- Peripheral blood smear may show characteristic sickled cells.

### ESR

- Elevated in infection, malignancy, and systemic vasculitis.

### Urine Dipstick

- Blood — used only for screening, must confirm presence of RBCs on microscopy.

- Leukocytes due to infection, inflammation
- Nitrites due to infection with urease-producing organisms
- Proteinuria suggests glomerulopathy.

#### **Urine Microscopy/Culture**

- RBCs—Hematuria > 3/hpf
- WBCs—Infection or inflammation
- Casts—White or red cell casts usually indicate medical causes of hematuria
- Crystals—Usually denote stone disease
- Cytology—For assessment of bladder cancer
- Culture—To confirm suspected infection, and AFB
- Hematuria with pyuria without bacteriuria (i.e. sterile culture) suggests renal TB
- Phase contrast microscopy—May be helpful in differentiating glomerular from lower tract hematuria (after excluding UTI).

#### **US**

- Often the first choice for renal imaging. It can differentiate cysts from solid lesions. The renal size, position, collecting system, prostate, and bladder can be visualized. Other abdominal and pelvic organs can also be assessed for their disorders
- Very helpful if the patient is allergic to IVP dye, has compromised renal function, and for evaluating hematuria in pregnancy
- In prospective studies, when US was combined with a single plain abdominal radiograph, it proved to be superior to urography as the primary imaging study in this series.<sup>8,9</sup>

#### **X-ray KUB**

- Plain X-ray can detect radiopaque calcium stones (>2 mm in size), occasionally cystine stones, and foreign bodies
- Radiolucent uric acid xanthine stones can not be detected.

## **INVESTIGATIONS — SPECIFIC**

### **Multichemistry Profile**

- Blood urea, creatinine, electrolytes, coagulation factors, ANA, and PSA to assess renal function; to exclude blood dyscrasias; collagen diseases, and to screen for prostatic carcinoma.

### **Hb Electrophoresis**

- To screen for sickle cell hemoglobin.

### **HRCT—KUB**

- The current procedure of choice for the detection of urinary tract calculi
- It can also detect diseases that are mistaken for renal colic, e.g. appendicitis, diverticulitis, AAA.

### **IVP/IVU**

- For evaluation of urolithiasis, renal tumors, bladder tumors, and renal trauma
- Studies have suggested that the omission of IVU as a routine investigation for painless hematuria does not dramatically reduce the detection rate of malignant conditions<sup>10</sup>
- Not indicated in patients with history of allergy to IV contrast and compromised renal function.

### **Cystoscopy**

- Important procedure to evaluate lesions affecting urethra and bladder mucosa; especially indicated in:
  - All patients older than age 40 with gross hematuria
  - Patients older than age 40 with negative microscopic hematuria, IVP, and US reports
  - Patients suspected of having bladder carcinoma even with negative IVP or cystourethrogram results.

### Urine for Schistosomiasis

- This diagnosis can be made after schistosome eggs are detected in 10 ml of urine, ideally collected between 10 am until 2 pm, passed through a polycarbonate membrane filter.

### Urine Cytology

- First void urine collected in the morning on three consecutive days enhances its sensitivity and specificity
- Indicated in all patients who have risk factors for renal carcinoma, especially in the evaluation of carcinoma *in situ*
- If malignant or atypical cells are identified, follow-up cystoscopy is indicated.

### Biopsy: Renal / Bladder/ Prostate

- Indicated in persistent hematuria with negative investigation findings, and evidence of progression (increasing proteinuria, creatinine, and blood pressure), and hereditary nephropathies<sup>11</sup>
- Bladder biopsy for evidence of malignancy, and granuloma (tubercular, sarcoid, schistosomiasis)
- Prostate malignancy.

### CLINICAL NOTES

- The red urine of hematuria must be distinguished from hemoglobinuria and myoglobinuria by demonstration of RBCs in the *freshly voided* urine. The presence of RBCs establishes the diagnosis of hematuria. If RBCs are absent, examination of the serum will distinguish hemoglobinuria from myoglobinuria. A sample of freshly voided urine is obtained and centrifuged. In hemoglobinuria (e.g. intravascular hemolysis due to sickle-cell disease, malaria), the supernatant will be pink; and in myoglobinuria

(e.g. muscle trauma, hypolipidemic drugs), the serum remains clear

- History should focus on any ingested substances (e.g. beets, food coloring agents, rifampicin, phenolphthalein, phenazopyridine) which may be the cause abnormal urine color, i.e. pseudohematuria, that can be mistaken for blood; awareness of such a possibility can spare further evaluation
- Type of hematuria (gross or microscopic), its relationship to urination or timing of hematuria, associated symptoms (recent sore throat, fever, chills, loin pain, and radiation) is important
- *Three tube test*—The source of hematuria may be ascertained by this test: predominantly, initial hematuria results from anterior urethral disease; final hematuria results from diseases of the bladder neck or the prostate gland; and hematuria throughout the stream suggests a lesion higher in the bladder, ureter, or kidney
- Menstrual history—It is important in women of childbearing age with history of blood in the urine to ascertain that bleeding is from the urinary tract and not vaginal in origin; catheterization may be required to differentiate vaginal bleeding from other sources
- Associated symptoms:
  - Painful hematuria is usually caused by UTIs, nephrolithiasis, renal infarction.
  - Hematuria with dysuria, frequency, urgency, and suprapubic pain usually denotes cystitis.
  - Hematuria occurring two to three days after a nonspecific infection of the upper respiratory tract suggests IgA nephropathy.
  - A rash, joint pain, photosensitivity, or Raynaud's phenomenon point to a collagen vascular disease.
  - History of bleeding elsewhere such as bruising of the skin or nose bleed indicates blood dyscrasias.

- Painless hematuria may signify primary renal disease such as tumor, polycystic kidney disease, or TB.
- Foul smelling vaginal or urethral discharge may indicate risky sexual behavior or presence of foreign body.
- Family history of nephrolithiasis, polycystic kidney disease, TB, or sickle-cell anemia suggests that these conditions as possible causes of hematuria. Hearing loss and renal failure in male members in the family is seen in Alport's disease. Hematuria without such disorders in the family members may suggest thin glomerular basement membrane disease (TBMD)
- Past history of travel to endemic areas (Schistosoma hematobium in Egypt); exposure to chemical carcinogens (aniline dyes, tobacco smoke) is suggestive of bladder tumor. History of medications, analgesic abuse (renal papillary necrosis), diabetes mellitus (nephrosclerosis), prostatic hypertrophy, trauma, etc. may be of diagnostic value
- Physical examination—Common findings associated with hematuria are given in Table 25.1.

## RED FLAGS

- Painless gross hematuria in an elderly, in the absence of infection, is caused by malignancy unless proved otherwise
- Hematuria in elderly, which may be transient, intermittent, or asymptomatic, always warrants a comprehensive evaluation to exclude malignancy
- Persistent hematuria warrants thorough evaluation when found in patients of any age
- Hematuria associated with *sterile pyuria* is genitourinary TB or interstitial nephritis until proved otherwise
- *Artifactual* hematuria<sup>12</sup> though rare, is common in people with Münchhausen syndrome, psychiatric patients, and drug addicts, suggesting renal colic. If suspected, requesting the person to void urine in presence of a witness clears the confusion.

## SELECTIVE GLOSSARY

**Alport's syndrome (hereditary nephritis)**—It is a genetic progressive nephropathy in which glomerular and other basement membrane

**Table 25.1:** Common signs associated with hematuria

System/organ	Disorder
<ul style="list-style-type: none"> <li>• Skin – petechiae, ecchymosis, lymphadenopathy, purpura on lower extremities</li> <li>• Fever, renal angle tenderness</li> </ul>	<ul style="list-style-type: none"> <li>• Blood dyscrasias, clotting disorder, Henoch-Schönlein purpura</li> <li>• Renal inflammation – pyelonephritis</li> </ul>
<ul style="list-style-type: none"> <li>• Fever, respiratory, flu-like illness</li> <li>• Fever, sore throat, edema, hypertension</li> </ul>	<ul style="list-style-type: none"> <li>• IgA nephropathy</li> <li>• Poststreptococcal glomerulonephritis</li> </ul>
<ul style="list-style-type: none"> <li>• Suprapubic tenderness</li> <li>• Bilaterally enlarged kidneys</li> <li>• Unilateral renal mass</li> </ul>	<ul style="list-style-type: none"> <li>• Bladder inflammation</li> <li>• Hydronephrosis, polycystic disease</li> <li>• Neoplasm – hypernephroma, cyst, hydronephrosis</li> </ul>
<ul style="list-style-type: none"> <li>• Hypertension, atrial fibrillation, valvular heart disease</li> </ul>	<ul style="list-style-type: none"> <li>• Glomerulonephritis, renal embolism, infarction</li> </ul>
<ul style="list-style-type: none"> <li>• Palpable bladder</li> </ul>	<ul style="list-style-type: none"> <li>• Urine retention due to BPH, prostate cancer</li> </ul>
<ul style="list-style-type: none"> <li>• Scrotal examination</li> <li>• Digital rectal examination</li> </ul>	<ul style="list-style-type: none"> <li>• Varicocele</li> <li>• Prostate disease – BPH, malignancy, pelvic trauma</li> </ul>
<ul style="list-style-type: none"> <li>• Hearing loss, hypertension, renal failure</li> </ul>	<ul style="list-style-type: none"> <li>• Alport's disease</li> </ul>

collagen is abnormal. The disease is inherited as an X-linked trait; in some families, however, autosomal recessive and perhaps autosomal dominant forms exist. The diagnosis of hereditary nephritis is based on: a positive family history (nephropathy, deafness particularly in male family members); audiometry, which detects high frequency deafness that is clinically not apparent; abnormalities of the eyes such as cataract, myopia; and renal biopsy (Bx). End-stage renal disease develops in persons 20 to 40 years of age.

**IgA nephropathy (Berger disease)**—It is a primary renal disease of IgA deposition in the glomerular mesangium, and a frequent cause of glomerular hematuria; occurs predominantly in men between the ages 20 and 30. An episode of gross (cola-colored urine), or microscopic hematuria 1 to 3 days after upper respiratory infection, or GI symptoms is the commonest presentation. Other findings include proteinuria, hypertension, and abnormal renal function tests. The serum IgA level is increased; serum compliment levels are usually normal, and the renal biopsy (Bx) is the standard for diagnosis.

**Thin Basement Membrane Disease (TBMD)**—It is also known as benign familial hematuria, — an autosomal dominant nephropathy defined by diffuse thinning of the glomerular basement membrane at electron microscopy examination (normal = 300 – 350 nm). Characteristic features include: glomerular hematuria, minimal proteinuria (<1.5 g/day), normal renal function, and familial occurrence. Though mostly benign, affected patient and family members should be followed up for progressive hypertension or disease progression.

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## CHAPTER

# 26

## Hemoptysis

### SYNOPSIS

*Hemoptysis* is defined as coughing up or expectoration of blood from the respiratory tract below the level of vocal cords, which can be from the trachea, major airways, or lung parenchyma, i.e. the tracheobronchial tree.

The amount of blood expectorated is important because the rate of bleeding is a major determinant of morbidity. The severity of hemoptysis has been arbitrarily divided as mild, moderate, or severe, depending upon the amount of bleeding. It is *mild* if less than 30 ml of blood is expectorated per day, or there is only streaking, or only flakes of blood in the sputum is present. Hemoptysis is *moderate* if bleeding is between 30 to 200 ml per day, and *severe* if bleeding occurs in excess of 200 ml per day. *Massive* hemoptysis has been variably defined as blood loss of 200 to 600 ml or more within 48 hours. Since any definition is arbitrary, especially because the quantity of blood expectorated is difficult to quantify, Ibrahim WH<sup>1</sup> has proposed the use of the term *life-threatening hemoptysis*; so as to avoid the difference of opinion (with regard to quantity of blood expectorated) applied to the general term *massive* which necessitates the identification of a

specific volume of blood. *Life-threatening hemoptysis* may thus be defined as any hemoptysis that: (1) is >100 ml in 24 hour; (2) causes abnormal gas exchange/airway obstruction; or (3) causes hemodynamic instability. The cut-off volume of 100 ml per 24 hours has been selected because it is the smallest amount of hemoptysis that is reported in literature to threaten the life of the patient.

Hemoptysis has been further classified as *single* if there is one episode of bleeding lasting up to seven days, but usually 1 to 2 days. It is called *recurrent* when the bleeding continues for longer than seven days or there is break in the continuity of at least 2 to 3 days. When pure blood without sputum is expectorated, it is called *frank* hemoptysis.

Considering that the anatomic dead space in the airway is 100 to 200 ml in most adult individuals, an amount of more than 300 ml. poses the risk of aspiration into the lungs. The threat to life is either by asphyxiation or exsanguination. However, hemoptysis of any degree and frequency needs thorough evaluation because even a small amount of hemoptysis may herald serious and incurable disease.<sup>2</sup> On the

other hand, even a moderate amount of hemoptysis is life-threatening in those with compromised respiratory system. Therefore, the aim of evaluation is three fold:

- Locate the site of bleeding
- Determine the underlying cause, and
- Decide the most suitable intervention/treatment if bleeding persists, recurs, or is massive, and when to treat.

Despite thorough evaluation, up to 30% of patients show no identifiable etiology of their hemoptysis; these patients are classified as having *cryptogenic hemoptysis*, which may be a harbinger of significant tracheobronchial pathology.<sup>3-5</sup>

## DIFFERENTIAL DIAGNOSIS

### Common

- Bronchitis (acute or chronic)
- Pneumonia (bacterial or viral)
- Tuberculosis (pulmonary)
- Bronchiectasis
- Bronchogenic carcinoma.

### Occasional

- Other primary lung neoplasms (carcinoid tumors: *vide infra* ↓↓)
- Metastatic malignancy
- Lung abscess
- Cardiovascular (CHF, mitral stenosis)
- Pulmonary embolism (PE)
- Systemic coagulopathy
- Pulmonary contusion or trauma.

### Rare

- Foreign body aspiration
- Parasitic infection (pulmonary amoebiasis, hydatid disease)
- Helminthic infection (paragonimiasis: *vide infra* ↓↓)

- Fungal infection (aspergillosis, pneumocystosis)
- Sarcoidosis
- Cystic fibrosis
- Pulmonary arterio-venous malformation
- Vasculitis (Wegener's granulomatosis, SLE)
- Cocaine lung ('crack' lung: *vide infra* ↓↓)<sup>6</sup>
- Factitious hemoptysis (*vide infra* ↓↓).

## INVESTIGATIONS—GENERAL

### CXR

- May provide important information suggesting the bleeding source by showing a lesion with bleeding potential such as : patchy areas of consolidation (pneumonitis); bilateral basal congestion (pulmonary edema); apical fibrocavitary lesion (TB); dilated bronchial walls (bronchiectasis); mass or coin lesion (neoplasm); or fungus ball in cavitary lesion (aspergillosis)
- However, additional follow-up testing (e.g. bronchoscopy, CT thorax) is recommended in patients presenting with hemoptysis in which the underlying cause was not detected at initial radiography, especially in those with risk factors : sex (male), age 50 years or older, and >40 pack year smoking history.<sup>7, 8</sup>

### Bronchoscopy

- This is the most important procedure for localizing the site of bleeding. Also, the bleeding sites may be sampled for histopathological analysis
- When to use rigid or flexible fiberoptic bronchoscopy or a combination of both is controversial.<sup>9,10</sup> Generally, rigid bronchoscopy is the preferred tool for massive hemoptysis because of its greater suctioning capacity of blood and clots, superior visualization of the major airways, and adequate ventilation and airway control

- Flexible bronchoscopy is preferable in patients with hemoptysis originating from the upper bronchi. Besides it can also be used to provide direct therapy in cases of continued bleeding
- Bronchoscopy is also indicated in cases of persistent or recurrent bleeding, and for smokers aged more than 40 years with a negative CXR study, because of the higher prevalence of lung cancer in this group.<sup>11, 12</sup>

#### **Sputum Gram Stain, AFB Smear, Culture, and Cytology\***

- Infecting organisms may be isolated such as in cases with pneumonitis, lung abscess, TB, or cytological features of malignancy may be present.

#### **CBC**

- Hb% reduced in chronic hemoptysis resulting in IDA
- Leukocytosis in upper and lower respiratory tract infections
- Eosinophilia in mycosis (allergic bronchopulmonary aspergillosis) or collagen-vascular disease (Churg-Strauss syndrome: *vide infra* ↓↓, PAN)
- Platelets decreased in thrombocytopenia.

#### **ESR**

- Elevated in infection, inflammation, and collagen-vascular disease.

#### **Coagulation Screen**

- Prothrombin time (PT) or partial prothrombin time (PPT) increased in disorders of coagulation, and in patients with anticoagulation therapy.

\*Molecular DNA technology (e.g. polymerase chain reaction) may be performed on cultured specimens to provide a more rapid and definitive diagnosis in mycobacterial infection.

#### **Mantoux Test**

- Used as an initial screening test in patients suspected with TB who have not received BCG immunization.

#### **ECG**

- Sinus tachycardia due to anxiety, and blood loss
- The classical S1 Q3 T3 pattern indicative of right heart strain with PE is rare; however, nonspecific ST segment and/or T-wave abnormalities are more common.

#### **Pulse Oximetry**

- To monitor for hypoxia.

### **INVESTIGATIONS—SPECIFIC**

#### **HRCT Scan**

- This procedure is of immense value for the detection of bronchiectasis and undiagnosed lung malignancy, i.e. when clinical suspicion for malignancy exists, but sputum and bronchoscopy reports are noncontributory or equivocal
- HRCT with IV contrast is presently considered as an adjunct diagnostic modality in patients with high probability of PE presenting with hemoptysis
- Current opinion favors HRCT to bronchoscopy as the first-line procedure for screening patients with large and those with massive hemoptysis.<sup>13-15</sup>

#### **Multidetector CT (MDCT)<sup>16-19</sup>**

- Multidetector row CT with 3D volume rendering has enhanced the conventional roles of thoracic CT. It permits noninvasive, rapid, and accurate assessment of the cause and consequences of hemorrhage into the

airways and helps guide subsequent management. It provides an excellent anatomy of the thorax, thereby increasing the diagnostic yield comprehensively. With the advent of MDCT, there is paradigm shift in vascular imaging from conventional catheter angiography to MDCT angiography, because this technique provides image quality that equals or surpasses that of conventional angiography. It is reliable in depicting clot and the pulmonary vasculature, and may also be used to evaluate thoracic venous anomalies (e.g. pulmonary arteriovenous malformations), and to plan therapy. In diffuse lung disease, this technique can increase nodule detection and help differentiate between small nodules and vessels. Recent advances in 3D volume rendering allow a fly through the tracheobronchial tree and the thoracic great vessels generating virtual endoscopic views in real-time.

#### D-dimer

- Used as an initial screening procedure; values lower than the cut off level (<500 mg/ml or 500 µg /l, by ELISA) rules out PE and obviate the need for other tests, e.g. pulmonary angiography.

#### Echocardiography

- To assess CHF with pulmonary edema and valvular heart disease such as mitral stenosis.
- Can be used to diagnose PE, especially with significant obstruction to pulmonary circulation.

#### V/Q Lung Scan

- Useful to diagnose PE although CT-pulmonary angiogram is the current gold standard.

#### c-ANCA (Classical or Cytoplasmic Antineutrophil Cytoplasmic Antibodies)

- Wegener's granulomatosis is associated with elevated levels.

#### HIV

- Positivity increases risk of pulmonary TB, and mycosis.

#### Lung Biopsy—(Bronchoscopic or Video-assisted Thorascopic Surgery, i.e. VATS).

- May be essential to diagnose malignancy (staging), sarcoidosis, and pulmonary fibrosis.

### CLINICAL NOTES

- The first step in evaluating hemoptysis is to ascertain that the blood is truly originating from tracheobronchial tree, and the underlying cause of bleeding. Bleeding from sources other than lower respiratory tract, i.e. upper airways and GI tract is called *pseudohemoptysis* (Table 26.1)
- If a clearcut source of the pseudohemoptysis cannot be determined, the spitting of blood is assumed to be true hemoptysis. The possible symptom associated causes of hemoptysis is given in Table 26.2
- The rate, amount of blood loss, and clinical stability of the patient are critical parameters to ascertain for any further evaluation. In patients with massive hemoptysis or in those with compromised respiratory functions, the urgent need is to prevent aspiration and stabilize the patient. The initial management in such situations is not diagnostic but therapeutic
- Characteristics of the sputum, in terms of color and odor may be helpful in defining the disease process causing hemoptysis: foul

**Table 26.1:** Difference between hemoptysis and pseudohemoptysis

<i>Clinical features</i>	<i>Hemoptysis</i>	<i>Pseudohemoptysis</i>
<ul style="list-style-type: none"> <li>• History</li> <li>• Origin of blood</li> <li>• Hematemesis and melena</li> <li>• Color of expectorated blood</li> <li>• Sputum examination</li> <li>• pH of expectorate</li> <li>• Microphages and neutrophils</li> <li>• Food particles in expectorate</li> </ul>	<ul style="list-style-type: none"> <li>• Dominant respiratory symptoms</li> <li>• Tracheobronchial tree; lung disease</li> <li>• Less likely</li> <li>• Bright red</li> <li>• Frothy usually</li> <li>• Alkaline</li> <li>• Present</li> <li>• Absent</li> </ul>	<ul style="list-style-type: none"> <li>• Respiratory symptoms less likely; other GI symptoms—nausea, vomiting, pain abdomen—more likely.</li> <li>• Oral cavity, larynx, esophagus; gastric or hepatic disease</li> <li>• More likely</li> <li>• Brown or black</li> <li>• Never or seldom</li> <li>• Acidic</li> <li>• Absent</li> <li>• Present</li> </ul>

**Table 26.2:** Symptoms to diagnose in patients with hemoptysis

<i>Symptoms</i>	<i>Causes</i>
<ul style="list-style-type: none"> <li>• Fever, cough—Dry/with sputum</li> <li>• Nausea, vomiting, melena, alcoholism, NSAIDs</li> <li>• DOE, orthopnea, pink frothy sputum</li> <li>• Cigarette smoking</li> <li>• Weight loss</li> <li>• Travel history</li> <li>• Cancer elsewhere</li> <li>• Association with menses</li> <li>• HIV, immunosuppression</li> <li>• Risk factors for aspiration</li> <li>• Trauma</li> <li>• Anticoagulant use</li> <li>• Recurrent hemoptysis, patient with a “fat” file</li> </ul>	<ul style="list-style-type: none"> <li>• URIs; bronchitis, pneumonia, lung abscess</li> <li>• Acid-peptic disorders; esophageal varices</li> <li>• CHF; mitral stenosis</li> <li>• Bronchitis; pneumonia; lung cancer</li> <li>• TB; COPD; lung cancer; HIV</li> <li>• TB, amebiasis, paragonimiasis</li> <li>• Metastatic malignancy</li> <li>• Pulmonary endometriosis (catamenial hemoptysis)</li> <li>• TB; neoplasia; Kaposi’s sarcoma</li> <li>• Lung abscess; foreign body aspiration</li> <li>• Iatrogenic lung injury</li> <li>• Medication effect</li> <li>• Factitious hemoptysis</li> </ul>

smelling sputum suggests a lung abscess; pink, frothy sputum is suggestive of pulmonary edema; slight blood streaking in the sputum is most common with bronchitis; frankly bloody sputum is seen in TB, PE, and bronchogenic carcinoma

- Associated symptoms—History of cough, dyspnea, sputum production over several years may suggest chronic bronchitis or bronchiectasis. Weight loss and fatigue may suggest an underlying malignancy; fever and night sweats might indicate TB
- History of smoking<sup>†</sup>, occupational exposures (e.g. asbestos, silica), drug abuse (crack lung), etc. are strong risk factors for massive hemoptysis

<sup>†</sup>Especially in a male sex, older than 40 years, and smoking history of more than 40 pack-years.

- History of coexisting disorders like cardiac (valvular disease, heart failure); renal (nephrotic syndrome); SLE; or previous malignancy may give clues to the cause of hemoptysis, which may indicate additional investigations to arrive at the diagnosis
- Hemoptysis since childhood is likely due to congenital heart defects, bronchiectasis, cystic fibrosis, or blood dyscrasias
- Hemoptysis that accompanies menstrual periods suggests pulmonary endometriosis
- Medications, especially anticoagulants, might contribute to bleeding. Patients belonging to this class of hemoptysis are those suffering from PE, cardiac valvular defects, or CHF
- Physical examination—Besides the vital signs (tachycardia, tachypnea, and hypotension

**Table 26.3:** Physical signs to diagnose in patients with hemoptysis

<i>Physical signs</i>	<i>Common causes</i>
<ul style="list-style-type: none"> <li>• Vital signs—Tachycardia, tachypnea, and hypotension</li> <li>• Oral cavity/ENT—Bleeding gums, epistaxis, oropharyngeal ulcers</li> <li>• Neck—Cervical and axillary lymphadenopathy</li> <li>• Skin—Ecchymosis or petechiae</li> <li>• Clubbing</li> <li>• Bronchial breath sounds</li> <li>• Localized reduced breath sounds/wheezing</li> <li>• Coarse crepts and rhonchi</li> <li>• Pleural rub</li> <li>• Tachycardia, raised JVP, S3 gallop, ankle edema, basal crepts</li> <li>• Rumbling mid-Diastolic murmur at apex</li> <li>• Tachypnea, loud P2</li> <li>• Horner's syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Hypovolemia</li> <li>• Poor oral hygiene; dental trauma; aphthous ulcer; bleeding disorder</li> <li>• TB; pulmonary or intrathoracic malignancy; pulmonary Kaposi's sarcoma</li> <li>• Systemic bleeding disorders</li> <li>• Bronchiectasis; lung abscess; bronchogenic carcinoma</li> <li>• Pneumonia</li> <li>• Bronchial carcinoma; foreign body</li> <li>• Bronchitis, bronchiectasis</li> <li>• Pneumonia; PE</li> <li>• CHF</li> <li>• Mitral stenosis</li> <li>• PE</li> <li>• Apical lung tumor; Pancoast tumor</li> </ul>

with hypovolemia) which are critical in stabilizing patients with massive hemoptysis, other common physical findings and their significance is given in Table 26.3.

## RED FLAGS

- Any male smoker with significant hemoptysis should have a CXR, particularly if associated with weight loss
- In an acutely breathless patient with hemoptysis, consider PE if there is no other obvious explanation for his symptoms. Indeed, no single symptom or sign or combination of clinical findings is suggestive of pulmonary thromboembolism;<sup>20</sup> further testing is required in the majority of patients
- TB is on the increase with rising incidence of HIV/AIDS infection; consider this possibility in every individual with risky sexual behavior
- Hemoptysis due to foreign body aspiration can remain undiagnosed for years and may lead to an incorrect diagnosis of asthma, bronchitis, or recurrent pneumonia. A high index of suspicion is the most important

factor in diagnosing foreign-body aspiration causing hemoptysis<sup>21</sup>

- Despite the most extensive investigations about 20-30% cases of hemoptysis remain undiagnosed. Such patients should be followed up closely for a period of time sufficient to exclude significant underlying disease such as bronchogenic carcinoma.<sup>22</sup>

## SELECTIVE GLOSSARY

**Carcinoid Tumor**—A type of slow growing neuroendocrine tumor, derived from primitive stem cell, usually benign, and found in the gastrointestinal system (most often in the appendix), and sometimes in the lungs or other sites; and characterized by attacks of severe flushing of the skin, diarrheal watery stools, bronchoconstriction, sudden drops in blood pressure, edema, and ascites. Symptoms are caused by tumor secretion of serotonin, prostaglandins, and other biologically active substances.

**Churg-Strauss syndrome (allergic granulomatosis and allergic angiitis)**—It is a disorder



that causes inflammation in blood vessels (vasculitis), which restricts blood flow to various organs. The disease can occur at any age, but it's more commonly diagnosed in middle-aged people. People older than 65 years are unlikely to develop Churg-Strauss syndrome. Although the disease may involve any organ, including lungs, skin, gastrointestinal system, kidneys, muscles, joints and heart, most commonly it affects lungs and skin. The restricted blood flow to these organs can cause temporary or permanent damage. There are three stages of Churg-Strauss syndrome, namely, *allergic (asthma, itching, polyp); hypereosinophilia (fever, weight loss, abdominal pain, GI bleeding); and systemic vasculitis (cough, dyspnea, diarrhea, hematuria)*. Churg-Strauss syndrome is progressive, but not everyone develops all three phases, and the phases don't always develop in order. Without treatment, this disease may be fatal.

**Cocaine lung**—Popularly called as *crack lung*, (the term *crack* characterizes the crackling sound heard when cocaine freebase is smoked); cocaine has multisystemic effects, and virtually every organ system may be a site of action. Crack lung, a syndrome usually occurring 1 to 48 hours after heavy cocaine smoking, is a hypersensitivity pneumonitis. It consists of the constellation of chest pain, cough with hemoptysis, dyspnea, bronchospasm, pruritus, fever, diffuse alveolar infiltrates without effusion, and pulmonary and systemic eosinophilia.

**Factitious hemoptysis (Münchhausen hemoptysis)**—When a patient presents with history of hemoptysis, especially recurrent hemoptysis with multiple normal reports from multiple hospitals, a factitious cause should be considered when the medical history or the patient's behavior is unusual. Most patients are young in age, and employees in the health care profession; they generally have a somewhat reasonable

medical history, but discrepancies are detectable upon careful evaluation. They usually and readily provide consent for all invasive procedures, including thoracotomy.

**Paragonimiasis (pulmonary)**—Caused by *Paragonimus westermani*, a common lung fluke in humans, commonly found in Asia, Africa, and Latin America. Human infections occur where local people consume improperly cooked freshwater crustaceans such as lobsters and crabs. Usually no symptoms are observed when the parasites migrate in the peritoneal cavity. When parasites invade the lung, several symptoms including pleuritic and chest pain, cough, and rusty sputum may be present. Pulmonary complications of untreated heavy infection include interstitial pneumonia, bronchitis, and bronchiectasis. Secondary complications may include bronchopneumonia, lung abscess, pleural effusion, or empyema. Ectopic paragonimiasis results in granulomatous lesions in the organs other than the lung. The most commonly affected organs include liver, spleen, omentum, and ovary. The most serious illness is cerebral paragonimiasis.

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## CHAPTER

# 27

## Hiccups

### SYNOPSIS

*Hiccups* (hiccough) or *singultus* may be defined as a complex reflex arc phenomenon characterized by involuntary, spasmodic contraction of diaphragm, and respiratory intercostal muscles, followed by abrupt closure of glottis, resulting in the characteristic 'hic' sound.

The reflex arc involves afferents, which travel along with the vagus and phrenic nerve fibers, the pharyngeal plexus (C2-C4), and the sympathetic chain (T6-T12) to the brainstem 'hiccup center'. The phrenic nerve (C3-C5) serves as the efferent pathway. Any irritation or stimulation along this reflex pathway (i.e. peripheral—involving the vagus or phrenic nerve and structures adjacent to the diaphragm, or central—involving the CNS) can result in hiccups (Table 27.1). Fluoroscopy reveals that only one hemidiaphragm is affected, with the left diaphragm being more frequently involved than the right, although bilateral involvement may occur.

Hiccups are a common part of life, and appear to serve no purpose in humans. It affects everyone, at any age—and *in utero*<sup>1</sup>—sometime or the other, with its frequency being between 4 and 60 per minute. Usually it is a short-lived annoyance that resolves spontaneously, or responds to one of several anecdotal remedies,

including a reported case of a man whose intractable hiccups lasting for four days completely ceased after sexual intercourse (i.e. ejaculation) with his wife.<sup>2</sup>

A hiccup bout is any episode lasting more than a few minutes. Chronic hiccups or those recurring as repetitive attacks are the ones needing medical attention. Based on its duration, hiccups are classified as:

- Acute—Any episode lasting up to 48 hours,
- Persistent or protracted—hiccups for >48 hours, and
- Intractable (diabolic)—hiccups for >1 month\*.

Though usually benign and self-limiting annoyance, they can be a major cause of distress, interrupting talking, eating, and sleeping, resulting in weight loss, exhaustion, and depression; occasionally it may even reflect serious underlying illness, often associated with organic conditions,

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\* The world record stands at 68 years, with a gentleman called Charles Osborne, USA, who hiccupped continuously from 1922 to 1990. The hiccups started in 1922 at a rate of 40 times per minute, slowing to 20 hiccups per minute and eventually stopping on June 5, 1990, a total of 68 years. Despite his condition, Osborne was able to lead a normal life, and was even married two times. It has been estimated that Osborne hiccupped 430 million times over the 68 year period. [ref. - [http://en.wikipedia.org/wiki/Charles\\_Osborne\\_\(hiccups\)](http://en.wikipedia.org/wiki/Charles_Osborne_(hiccups))].

**Table 27.1:** Common causes of hiccups

CNS	Infection (meningitis, encephalitis) Intracranial tumor Stroke, basilar artery insufficiency Trauma Surgery AV malformation Multiple sclerosis
Metabolic	Toxic (alcohol, drug abuse) Uremia Electrolyte imbalance Diabetic ketoacidosis Hyperventilation (hypocapnia)
Irritation of vagus or phrenic nerve and branches at the level of:	
Head and neck	Foreign body in the ear Goiter Cervical tumor
Thorax	Gastric distension Pneumonia Empyema Pleurisy Gastroesophageal reflux disease Esophageal obstruction Mediastinal tumor Inferior wall myocardial infarction Pericarditis Aneurysm
Abdomen	Gastric distension Subdiaphragmatic abscess Bowel obstruction Hepatomegaly Hepatitis Cholecystitis Pancreatitis Pancreatic malignancy Peritonitis Tumor
Surgical	General anesthesia, postoperative
Psychogenic	Stress, excitement, hysteria

specially advanced tumors of the digestive tract.<sup>3</sup> Symptomatic relief to the exasperated patient while conducting a judicious evaluation to determine the cause is the initial approach in the management with persistent hiccups.

## DIFFERENTIAL DIAGNOSIS

### Common

- Abdominal distension (aerophagy, carbonated beverages, excess smoking, hurried-eating)

- Sudden emotional excitement (laughing)
- Sudden temperature changes (hot then cold liquids, hot then cold shower)
- Psychogenic (anxiety)
- Alcohol excess (acute or chronic).

### Occasional

- Metabolic (Uremia, diabetic ketoacidosis, electrolyte imbalance)
- Neck (goiter)
- Thorax (pneumonia, reflux esophagitis, cardiomegaly)

- Abdomen (subphrenic abscess, hepatitis, hepatomegaly, cholecystitis, paralytic ileus)
- CNS infection (meningitis, encephalitis).

**Rare**

- Drugs (high dose steroids, benzodiazepines)<sup>4, 5</sup>
- Toxemia (hyperpyrexia, septicemia, peritonitis)
- Neoplasms (head and neck, esophagus, mediastinum, gastric, hepatic, pancreatic)
- Thorax (pericarditis, inferior wall myocardial infarction)
- CNS (stroke, multiple sclerosis)
- Foreign body in ear
- Head trauma
- Psychogenic (neurosis, hysteria).

**INVESTIGATIONS—GENERAL****CBC, Blood Film**

- Leukocytosis in infection, e.g. subphrenic abscess, pneumonia
- Malarial parasites may be seen on blood film in patients with pyrexia as a cause of hiccups.

**ESR**

- Elevated in infection, malignancy.

**Urea/Creatinine**

- Elevated in uremia.

**Electrolytes—Na, K, Ca**

- Hyponatremia, hypokalemia, hypocalcemia, hypercalcemia, and hyperglycemia can precipitate hiccups
- A study shows that for every 10 mEq/l reduction in serum sodium, patients likely to be 17 times at risk of developing hiccups.<sup>6</sup>

**LFT**

- ALT, AST values elevated in hepatitis, and cirrhosis

- Alkaline phosphatase elevated in hepatic obstruction.

**Fluoroscopy of Diaphragmatic Movement**

- Confirm diagnosis if malingering suspected
- Determine if unilateral or bilateral before invasive therapy, e.g. phrenic nerve block surgery or phrenic nerve or diaphragmatic pacing.

**CXR**

- Consolidation, cavitation, hilar mass, mediastinal mass, effusion, and collapse due to various causes such as pneumonia, malignancy, lymphoma, and aneurysm may be noted as etiological factors
- Elevation of a hemidiaphragm may be due to phrenic nerve palsy from carcinomatous infiltration, diaphragmatic hernia, or hepatomegaly on right side may be seen.

**ECG<sup>7</sup>**

- In patients suspected with MI, arrhythmia, pericarditis.

**INVESTIGATIONS—SPECIFIC****EGD**

- To evaluate in patients with reflux, acid-peptic disorder, and esophageal carcinoma.<sup>8</sup>

**US Abdomen**

- To evaluate diaphragmatic movements, and subdiaphragmatic, hepatic, and gallbladder lesions.

**CT Scan Chest**

- To define and identify pulmonary infection, tumors, mediastinal mass, and aortic aneurysm.

**MRI Brain<sup>9</sup>**

- Indicated in patients with intractable hiccups (with or without neurological signs), e.g.

raised intracranial pressure (with contraindication to lumbar puncture), intracranial bleeding, tumor, multiple sclerosis, and encephalitis

- To differentiate psychogenic hiccup from neurological disorder.

### Bronchoscopy

- May be indicated to confirm a suspected lung neoplasm with CT/MRI of chest with subsequent biopsy (Bx).

### Echocardiography

- To rule out pericardial effusion, pericarditis.

### CSF

- In patients suspected with meningitis, and encephalitis.

## CLINICAL NOTES

- Hiccups commonly occur as an isolated brief symptom; they self-terminate or respond to simple maneuvers, and need no investigation or follow-up care.
- In contrast, patients with persistent hiccups require thorough evaluation as they are frequently associated with underlying pathological process, mostly related to respiratory, abdominal, and nervous systems. Therefore, the history and examination should be focused similarly.
- History includes—Onset, duration, associated symptoms and events (Table 27.2), alcohol and drug abuse, surgery (craniotomy, thoracotomy, laparotomy), and past history of hiccups and its treatment.

**Table 27.2:** Symptoms and signs of common pathologic disorders associated with hiccups

<i>Symptoms and signs</i>	<i>Possible disorders</i>
<ul style="list-style-type: none"> <li>• Cough, sputum, fever, chest pain; lung consolidation, effusion, pleural rub</li> <li>• Above symptoms, dyspnea, weight loss, with possible hemoptysis in a smoker; clubbing, lymphadenopathy</li> <li>• Above symptoms, stridor, hoarse voice, neck/chest swelling, engorged veins over chest and neck, night sweats; Horner's syndrome</li> <li>• Bovine cough, hoarse voice, stridor, weight loss; neck mass</li> <li>• Heartburn, regurgitation</li> <li>• Progressive dysphagia, dyspepsia, weight loss</li> <li>• Pain abdomen, referred to shoulder/scapula, fever,</li> <li>• Alcohol excess, icterus, back pain, weight loss,</li> <li>• Headache, neck stiffens, fever, altered consciousness, seizures</li> <li>• Sudden onset headache, aphasia, visual defects, motor/sensory deficit</li> <li>• Oliguria, edema, hypertension</li> <li>• Amelioration of hiccups by sleep, bizarre accompanying symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Pneumonitis</li> <li>• Bronchial tumor</li> <li>• Extrinsic compression by mediastinal mass (lung carcinoma, lymphoma, aortic aneurysm, retrosternal goiter, dermoid cyst)</li> <li>• Intrinsic laryngeal lesion/Extrinsic compression (benign/malignant)</li> <li>• Gastroesophageal reflux disease, hiatal hernia, acid-peptic disease</li> <li>• Esophageal compression (carcinoma of the esophagus), carcinoma stomach</li> <li>• Cholecystitis, hepatitis, subdiaphragmatic abscess</li> <li>• Hepatomegaly, pancreatitis/malignancy</li> <li>• Meningitis, encephalitis, CNS mass lesion</li> <li>• Stroke, basilar artery insufficiency</li> <li>• Uremia</li> <li>• Hysteria</li> </ul>



- Physical examination includes head, neck (thyroid, lymph nodes, neck vessels), ear (tympanic membrane irritation by foreign body), chest (consolidation, pleural effusion), abdomen (hepatomegaly, mass, distension), and CNS for neurologic deficit.
- Presence of hiccups during sleep usually indicates an underlying organic cause; whereas its absence during sleep indicates a psychogenic or idiopathic etiology.
- Pathologic laughing occurs in approximately 10% of patients with multiple sclerosis, especially when patients have entered the chronic stage.<sup>10</sup>

### RED FLAGS

- Although *benign* hiccups occur less frequent in adult life, *intractable* hiccups are more common in adult life
- Exclude multiple sclerosis in any patient with persistent hiccups as psychogenic, especially in young adults
- Persistent hiccups are reported to be an early manifestation of rare disorders such as Addison's disease,<sup>11</sup> Parkinson's disease,<sup>12</sup> SLE,<sup>13</sup> and herpes zoster<sup>14</sup>
- Drug-induced hiccups are a known phenomenon; hence suspect any medication that a patient may be taking as a cause for persistent hiccups
- In a patient with hiccups and hypercalcemia, prompt work up is indicated to rule out malignancy, notably breast and lung cancer and multiple myeloma.

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## CHAPTER

# 28

## Insomnia

### SYNOPSIS

*Insomnia*, commonly understood as insufficient or unrestorative sleep, is a subgroup of various types of sleep disorders\* as defined by DSM-IV-TR system.

The profile of insomnia differs from patient to patient, and may even change over time within a given patient. It is therefore important to carefully categorize the individual's sleep disorder. Specifically, insomnia is known as, 'Disorder of Initiation and/ Maintenance of Sleep, i.e. *DIMS*. As is evident, insomnia consists of two components: difficulty in initiating sleep (going off to sleep) and difficulty in maintaining sleep (remaining asleep).

Clinically, insomnia is classified as:

- *Transient* insomnia—lasting for few nights such as change in sleep schedule or environment,

- *Short-term* insomnia—lasts for few days to three weeks, e.g. medical illness, protracted stress, and
- *Long-term* insomnia (chronic insomnia)—insomnia occurring at least three times per week for more than four weeks, and that it causes either marked distress or interference with social or occupational functioning.

According to DSM-IV-TR criteria, *primary* insomnia is sleeplessness that is not attributable to a medical, psychiatric, or environmental cause. Additionally:

- The predominant symptom is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.
- The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- The sleep disturbance does not occur exclusively during the course of narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, or a parasomnia.
- The disturbance does not occur exclusively during the course of another mental disorder (e.g. major depressive disorder, generalized anxiety disorder, a delirium).

\*Sleep disorders include 4 general groups: 1—Primary Sleep Disorders; 2—Dyssomnias - (a) - insomnia, i.e. *DIMS*; and (b)- Hypersomnia(i.e. disorders of excessive sleepiness such as narcolepsy, sleep apnea, Kleine-Levin syndrome, nocturnal myoclonus, e.g. restless legs syndrome, periodic limb movement disorder); 3—Parasomnias (i.e. abnormal behaviors during sleep such as somnambulism, night-terrors, nightmares, enuresis); and 4—Sleep Disorder Related to Another Mental Disorder (i.e. secondary to medical/psychiatric disorders).

- The disturbance is not due to the direct physiological effects of a substance (e.g. drug abuse, medication) or a general medical condition. Conversely, *secondary* insomnia may arise from several recognizable sources.

Patients with insomnia may present with nonspecific or unusual symptoms. They range from fatigue, lack of concentration, headache, irritability, myalgias, GI upset, problems with interpersonal relationship, and overall decreased quality of life.

Most insomnia is transient or short-term in duration; their diagnosis based mainly on historical and physical findings. In problematic or chronic insomnia, review of medical and psychiatric history, and full polysomnography in a sleep laboratory may be essential to determine the source of sleep difficulty.

## DIFFERENTIAL DIAGNOSIS

### Common

- Sleep preoccupation ('trying too hard to sleep', unnecessary concern about inability to sleep)
- Poor sleep hygiene
- Biorhythm disruption (jet lag syndrome, work shift change)
- Psychosocial stressors (bereavement, family-related stress)
- Pain of acute/chronic physical illness (injury, pyrexia, headaches, arthritis)
- Psychiatric (anxiety, depression)
- Substance abuse (alcohol, caffeine, cocaine, nicotine, benzodiazepines)
- Substance withdrawal (rebound insomnia)
- Medications (decongestants, bronchodilators, OTC agents)
- Chronic fatigue syndrome (CFS: *vide infra* ↓↓).

### Occasional

- Cardiac (PND, LVF)
- Respiratory (asthma, COPD)
- Gastrointestinal (GERD)
- Endocrine (hyperglycemia, hyperthyroidism, perimenopause)
- Renal (prostatism, BPH)
- Neurological (peripheral neuropathy, dementia, psychosis, seizures, PD).

### Rare

- Sleep apnea syndrome (central and obstructive: *vide infra* ↓↓)
- Mental disorders (mania, hypomania, and schizophrenia)
- Fatal familial insomnia (FFI: *vide infra* ↓↓).

## INVESTIGATIONS—GENERAL

### CBC

- Erythrocytosis may be seen in patients with obstructive sleep apnea (OSA), or chronic lung disease.

### TFTs

- As indicated in hyperthyroidism.

### ECG

- For evidence of cor pulmonale and cardiac arrhythmias.

### Pulse Oximetry<sup>1-4</sup>

- Nocturnal oxygen desaturation (NOD)—Evaluation of NOD may be used as a screening test in patients with a high probability of OSA or sleep disordered breathing. The absence of desaturation (at the rate of at least 10 to 15 events per hour) may be used to exclude OSA
- NOD may be an important contributor to IHD, coronary restenosis in patients treated with stent placement, and metabolic syndrome.

## INVESTIGATIONS—SPECIFIC

### Sleep Diary<sup>†</sup>

- Maintained for a period of two weeks to collect information on bedtime and time of rising, duration and quantity of sleep, timing and quantity of meals and exercise, and ingestion of alcohol, drugs, and caffeine. The findings are correlated with the patient's subjective assessments of insomnia, and help to determine sleep pattern of the patient, its severity, and causes; and also provides educative value to learn more about sleep hygiene
- Other tools that may be used to assess insomnia include—Epworth Sleepiness Scale<sup>‡</sup>, Sleep disorders questionnaire<sup>§</sup>, Insomnia Severity Inventory, and the Pittsburgh Sleep Quality Index<sup>\*\*</sup>.

### Polysomnography (Sleep Study)

- It involves monitoring and staging sleep, i.e. by recording brain waves with EEC, eye movements with electrooculogram (EOG), and chin movements with EMG; breathing patterns, e.g. airflow, respiratory effort, pulse oximetry, heart rate; limb movements, e.g. of the legs and occasionally arms with EMG, and body position. Most patients are also monitored with remote audio and video recordings to observe for behaviors and seizures. Polysomnography is used in special circumstances, e.g. to exclude primary sleep disorders.

<sup>†</sup>Available at: [http://www.helpguide.org/life/pdfs/sleep\\_diary.pdf](http://www.helpguide.org/life/pdfs/sleep_diary.pdf); [http://content.revolutionhealth.com/contentfiles/media-pdf-hw-form\\_tm4434.pdf](http://content.revolutionhealth.com/contentfiles/media-pdf-hw-form_tm4434.pdf); and <http://www.shuteye.com/sleep-solutions/sleep-patterns/sleep-diary.aspx>

<sup>‡</sup><http://www.reliamed.com/Forms/SleepinessScale.pdf>

<sup>§</sup><http://www.tmj-sleep-pain.com/sleep-disorders.htm>

<sup>\*\*</sup>[http://www.consultgerirn.org/uploads/File/trythis/issue06\\_1.pdf](http://www.consultgerirn.org/uploads/File/trythis/issue06_1.pdf)

### Actigraphy<sup>5</sup>

- A new technique that records individual's activities during sleep and waking; useful in the diagnosis of primary sleep disorders, hypersomnia, and parasomnia.

### CT/MRI Brain

- In special circumstances such as history of trauma, Alzheimer's disease, PD, MS, seizure disorder, and mass lesion.

### Mini-Mental State Examination (MMSE) and Geriatric Depression Scale

- In elderly patients these procedures may be necessary to identify comorbid conditions such as dementia and depression which often result in insomnia.

### Drug Toxicology Screen

- In occult cases of insomnia suspected to be due to substance abuse.

## CLINICAL NOTES

- History—A comprehensive sleep history obtained from both the patient and the patient's bed partner is an important component in the initial evaluation of insomnia (Table 28.1)
- History should focus on age, onset and duration, patient's perception of sleep problem, coping mechanisms, day-time naps, occupation, lifestyle, family and work-related stress, habits, travel, medications, addiction, and any medical illness. This step helps to eliminate insomnia due to another medical, psychiatric, substance abuse or circadian rhythm disorder
- Nocturnal symptoms<sup>6</sup>—A specific enquiry should be made from the patient as well as bed-partner about 'nocturnal' symptoms giving rise to transient or chronic insomnia. These include respiratory distress, snoring,

**Table 28.1:** Taking a sleep history**General**

- Chief complaint, i.e. Nature of specific sleep problem
- Onset, duration, and course of the symptoms
- Psychiatric/medical history
- Life events/current social status
- Drug use (prescribed or illicit)
- Daily routine, dietary habits, lifestyle
- Sleep diary data assessment, if maintained
- Recent weight gain/loss (diabetes mellitus, thyroid disorder, depression)
- Sleep environment (TV, noise, lights)
- Family h/o sleep disorders (FFI).

**Night time**

- Do you go to bed at the same time every night?
- How long does it take to fall asleep? (Sleep latency; related to initiating sleep—due to poor sleep hygiene, stimulant medications, drugs, etc.)
- Quality of sleep - sound sleep? Disturbed—Frequent wake ups?
- What do you do when you wake up at night? Watching TV? Reading? Take sedatives?
- Duration of sleep—estimated time spent sleeping at night (related to remaining asleep—due to alcohol, anxiety, depression, asthma, BPH, etc.)
- Do you snore, feel choked-up, or wake-up confused? (OSA)
- Does your legs or arms jerk/kick during sleep? (PLMS)
- Do you experience ‘creeping, crawling feeling’ in the legs? (RLS)

**Day time**

- Are your waking times regular?
- Do you feel refreshed on waking? (depression)
- Do you take naps in the daytime?
- Time of napping, and its duration (excessive daytime somnolence)
- Do you fall asleep while driving, reading, watching TV, or talking to friends? (narcolepsy)

**Questions for the sleep partner: Does he or she complain of patient's:**

- Loud snoring, gasping, choking, or at times stop breathing? (OSA)
  - Legs and arms jerk/kick during sleep (PLMS)
  - Temporary inability to talk or move when falling asleep or awakening? (sleep paralysis, cataplexy)
- [PLMS—periodic limb movement syndrome; RLS—restless leg syndrome]

gasping (OSA); jerking of feet and legs (periodic limb movement disorder: *vide infra*:↓↓); and dyspepsia, cough, chest discomfort (GERD, CAD). Symptoms such as

bed-wetting, sleepwalking, night terrors, night mares, etc. are typical of parasomnias

- Physical findings such as obesity, hypertension, large neck, large tongue, or abnormalities in the ear-nose-throat examination may be associated with OSA. Signs of psychiatric disorders and medical diseases related to coronary disease, obstructive respiratory disease, and neurologic system should be evaluated<sup>7</sup>
- Sleep apnea when suspected needs further evaluation of the predisposing factors for obstruction to airways, including enlarged tonsils and adenoids, micrognathia, macroglossia, and endocrinopathies such as hypothyroidism and acromegaly
- Although the need for sleep does not necessarily decrease with age, the incidence of sleep dysfunctions increases with age which are normally related to pathologic processes that are associated with aging, e.g. OA, LVF, BPH, and psychiatric disorders
- Although insomnia is commonly viewed as a symptom of anxiety and depression, studies indicate that it often predates the emergence of these disorders, suggesting that insomnia treatment could possibly prevent psychiatric morbidity.

**RED FLAGS**

- An insomniac should be differentiated from a *short sleeper* who needs less than six hours of sleep per night and has no symptoms or dysfunction
- Potentially serious problems may be associated with OSA such as systemic and pulmonary hypertension, cor pulmonale, tachyarrhythmias, and IHD
- In patients with sleep apnea associated with CNS disfunction, consider intracranial lesion (e.g. thalamic tumor), nocturnal seizures and drug abuse.



## SELECTIVE GLOSSARY

**Chronic fatigue syndrome (CFS)**—It is a clinical diagnosis characterized by an unexplained, persistent or relapsing chronic fatigue that is of at least six months' duration, and characterized by four or more of the following symptoms present concurrently for at least six months, namely: impairment of memory or concentration; diffuse pain; sore throat; tender lymph nodes; new headaches; and nonrestorative sleep. Infectious, immunological, neuroendocrine, sleep, and psychiatric mechanisms have been proposed as etiological factors; however, a unifying etiology for CFS has yet to emerge. Clinical evaluation is based upon above standardized guidelines, including an assessment of functional impairments. Since there are no specific diagnostic tests or biological markers for CFS, the diagnosis is made by ruling out other causes of fatigue such as eating disorders, psychotic disorders, bipolar disorder, melancholic depression, and substance abuse within 2 years of the onset of fatigue. Trigger points, which suggest fibromyalgia, are absent in patients with CFS and fibromyalgia rarely coexist in the same patient.

**Fatal familial insomnia (FFI)**<sup>8</sup>—Fatal familial insomnia is a rare inherited autosomal dominant disorder characterized by degeneration of the thalamus and progressive insomnia. It is caused by a mutation in the prion protein. Patients present in their 50's with a progressive sleep disorder. There may be autonomic dysfunction. Dementia and death usually occur within one year following presentation. Measuring the cerebral metabolic rate of glucose (CMRglc) with 2-[18F] fluoro-2-deoxy-D-glucose PET in parallel with detailed clinical, neuropsychological examinations and polysomnography with EEG spectral analyses may help in presymptomatic diagnosis of FFI.

**Obstructive sleep apnea (OSA)**—It is characterized by episodes of partial or complete closure

of the upper airway that occur during sleep and lead to breathing cessation (defined as a period of apnea > 10 sec) despite persistent respiratory efforts. Symptoms include restlessness, snoring, recurrent awakening, morning headache, and excessive daytime sleepiness. Anatomic risk factors include obesity, an oropharynx "crowded" by a short or retracted mandible, a prominent tongue base or tonsils, a rounded head shape and a short neck, a neck circumference > 43 cm, thick lateral pharyngeal walls, or lateral parapharyngeal fat pads. Other identified risk factors include postmenopausal status, aging, and alcohol or sedative use. A family history of sleep apnea is present in 25 to 40% of cases. Many people with OSA have disorders such as hypertension, stroke, diabetes, gastroesophageal reflux disease, nocturnal angina, heart failure, acromegaly, and hypothyroidism. OSA can also be associated with cardiac arrhythmias (e.g. bradycardia, asystole). Diagnosis is based on sleep history, and polysomnography.

**Periodic limb movement disorder (PLMD)**—It is characterized by bilateral repeated, rhythmic, small-amplitude jerking or twitching movements in the lower extremities and, less frequently, in the arms. These movements occur every 20 to 90 seconds, mainly in nonrapid eye movement sleep, and can lead to arousals, which are usually not perceived by the patient. Rather, the presenting complaint is poor sleep and daytime somnolence.

Occasionally, a bed partner may provide the history of limb movements.

Physical and neurological examinations are normal. In some cases, excessive somnolence may be noted. Definitive diagnosis requires polysomnography.

This condition and restless legs syndrome are more common in older patients.

**Restless Legs Syndrome (RLS)/Ekbom syndrome**—A disorder characterized by: (1) a



desire to move the limbs, often with paresthesias or dysesthesias; (2) symptoms exacerbated by rest and relieved by activity; (3) motor restlessness; and (4) nocturnal increase in severity of symptoms. Most patients, however, simply relate a vague, nonpainful, indescribable discomfort in the limbs and use terms, such as crawling, creeping, jittery, tingling, burning, itching, aching, etc. The unpleasant limb sensations are precipitated by rest or inactivity, especially in bed at night or in the car, airplane, theater, etc. Motor activity characteristically relieves the limb discomfort. Most patients notice worsening of symptoms in the evening, usually in bed before sleep or in the middle of the night, followed by improvement early in the morning. In severe cases, patients experience symptoms both in the day and night. Although RLS is idiopathic in most cases, it can be associated with several conditions, particularly iron, folate, and B<sub>12</sub> deficiency. The possible secondary causes of RLS include cigarette smoking, varicose veins, hypothyroidism or hyperthyroidism, acute intermittent porphyria; myelopathy or myelitis, carcinoma, and drug withdrawal from vasodilators, sedatives, imipramine, or opiates. This condition may be associated with uremia, diabetes mellitus, and rheumatoid arthritis. The diagnosis of RLS rests largely on clinical history. Polysomnography is rarely necessary.

**Sleep apnea: central**—A condition associated with multiple episodes of sleep apnea which are distinguished from obstructive sleep apnea (OSA) by the complete cessation of efforts to breathe. This disorder is associated with dysfunction of central nervous system centers that regulate respiration or cardiac dysfunction. This condition may be idiopathic (primary) or associated with

lower brainstem lesions, stroke, Parkinson's disease, COPD, CHF, diabetes mellitus, thyroid disease, medication effect, and other conditions. The most common reported symptoms are insomnia, frequent awakenings, a nonrestorative sleep, choking, shortness of breath, and excessive daytime sleepiness or fatigue. Sometimes, bed partners report witnessed apneas and mild snoring. The laboratory findings are not helpful. Primary central sleep apnea is frequently associated with OSA. When both forms are present the condition is referred to as mixed sleep apnea, i.e. *sleep apnea syndrome*.

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## CHAPTER

# 29

## Jaundice

### SYNOPSIS

*Jaundice* (icterus) is yellowish discoloration of the tissues, noticed especially in the skin, sclera\*, and mucous membrane, due to excess accumulation of bilirubin—a reddish pigment of heme metabolism.

Hyperbilirubinemia may be due to excessive hemoglobin degradation/bilirubin overproduction, defective hepatic uptake/conjugation, or impaired excretion of bilirubin by the hepatobiliary system; i.e. interruption of the breakdown pathway at any of a number of steps—from hemoglobin breakdown to uptake by the hepatocellular membrane to excretion into the biliary system—will result in jaundice, with an increase in serum bilirubin.

Patient occasionally present with complaints of 'turning yellow'; usually the symptoms of jaundice (excluding those in whom it is secondary to hemolysis) referred by the patient are nonspecific, such as loss of appetite, nausea, vomiting, pain abdomen, lack of taste, lethargy,

high colored urine (due to increased glomerular filtration of conjugated bilirubin), pale stools (as excretion of bilirubin into the intestine is decreased), itching skin (presumably from the deposition of bile salts), etc.

Very often family members notice a yellow discoloring of the sclera or skin before the patient notices. This objective or clinical jaundice is usually evident when the serum (conjugated) bilirubin reaches 2-4 mg/dl (40-80  $\mu\text{mol/l}$ ). Because elastin has a high affinity for bilirubin, and scleral tissue is rich in elastin, jaundice is best detected by examining the sclerae; a second place to examine is underneath the tongue, i.e. frenulum of the tongue. As jaundice deepens, the skin color may change from a yellow tinge to deep yellow and eventually, in long standing jaundice (e.g. chronic extrahepatic biliary obstruction, primary biliary cirrhosis), to a greenish hue due to oxidation of bilirubin to biliverdin.

Although jaundice in adults is typically classified into prehepatic (due to hemolysis), hepatocellular (due to intrinsic liver disease), and cholestatic (obstructive—intrahepatic or posthepatic cholestasis) jaundice (Table 29.1), multiple mechanisms may be operative simultaneously; for instance in patients with

\* The usual term *scleral icterus* is misleading, since bilirubin is actually deposited in the vascular conjunctiva rather than the avascular sclerae. (Talley NJ et al. Clinical examination: A Systematic Guide to Physical Diagnosis 2006, 5th ed. p.18).

**Table 29.1:** Clinical approach to the patient with jaundice<sup>#</sup>

Diagnostic factors	Type of jaundice			
	Hemolytic	Hepatocellular	Intrahepatic cholestatic	Extrahepatic cholestatic
Symptoms	Mild jaundice; may be asymptomatic or back-ache, joint pain	Nausea, vomiting, fever, anorexia	Deep jaundice, dark-colored urine, light-colored stools, pruritus	Deep jaundice, dark-colored urine, light-colored stools, pruritus, cholangitis, biliary colic
Physical findings	Pallor; splenomegaly	Tender hepatomegaly, splenomegaly*	Tender hepatomegaly	Hepatomegaly, palpable gallbladder, abdominal mass
<i>Liver tests</i>				
Bilirubin				
Total	<6 mg/dl	Variable	Variable, may be >30 mg/dl	<30 mg/dl
Direct (i.e. conjugated)	<20%	>50%	>50%	>50%
Alanine aminotransferase	Normal	>5-fold increase	2- to 5-fold increase	<2- to 3-fold increase; >3- to 5-fold increase with cholangitis
Alkaline phosphatase	Normal	<2- to 3-fold increase	>3- to 5-fold increase	>3- to 5-fold increase
Prothrombin time	Normal	Prolonged	Prolonged	Prolonged
Corrected by vitamin K	.....	No	Variable	Yes
<i>Ultrasonography of liver</i>				
Biliary dilatation	No	No	No	Yes
Endoscopic retrograde cholangiopancreatography	Not necessary	Not necessary	Usually not necessary	Usually necessary

\*May or may not be present.

<sup>#</sup> Source: Kamath Patrick S. Clinical Approach to the Patient with Abnormal Liver Test Results. Mayo Clin Proc 1996; 71:1089-95.

acute hepatitis, cirrhosis, prolonged biliary tract obstruction, familial and immaturity defects, jaundice may result due to both intrinsic hepatocellular failure as well as hemolysis. In general, however, one mechanism predominates, so that knowledge of the predominant form of plasma bilirubin (conjugated or unconjugated) is of value in evaluating possible causes of hyperbilirubinemia.<sup>1</sup>

## DIFFERENTIAL DIAGNOSIS

### Common

- Acute viral hepatitis (A, B and C)
- Alcoholic liver disease (cirrhosis)
- Extrahepatic obstruction (gallstones)
- Organ infection (cholangitis, cholecystitis, liver abscess, chronic pancreatitis).

### Occasional

- Secondary to systemic infections (malaria; HIV; leptospirosis; infectious mononucleosis; cytomegalovirus, i.e. CMV; Epstein B virus, i.e. EBV; herpes zoster virus, i.e. HZV; herpes simplex virus, i.e. HSV; yellow fever)
- Autoimmune hepatitis (i.e. chronic active hepatitis)
- Hepatic carcinoma (i.e. primary hepatoma)
- Secondary hepatic carcinoma (from breast, stomach, bowel, lung, pancreas, and ovary).

### Rare

- Hemolysis (hemolytic anemia, G6PD deficiency, sickle cell disease, thalassemia, ABO/Rh incompatibility)
- Biliary obstruction (stricture, cyst, malignancy)

- Drug toxicity (paracetamol, erythromycin, rifampicin, isoniazid, oral contraceptives, anabolic steroids, statins, methotrexate, phenothiazine, halothane)
- Hereditary disorders (Gilbert's disease, Crigler-Najjar syndrome, Wilson's disease).

## INVESTIGATIONS—GENERAL

### CBC

- Anemia—in hemolysis, bleeding, malignancy
- Reticulocytosis—in hemolysis
- WBC—leukocytosis in infection, such as hepatitis, cholangitis
- PS—atypical lymphocytes may be seen in infectious mononucleosis.

### ESR

- Elevated in infection, malignancy.

### Urinalysis<sup>2</sup>

- Presence of *bile pigments*, i.e. *bilirubinuria* suggests conjugation is taking place. Bilirubinuria is the earliest abnormality in hepatitis. It is present even when the serum bilirubin is normal. Hence, bilirubinuria in a febrile patient is diagnostic of hepatitis. Late in the course of the disease, when *deltabilirubin* is formed, the test becomes negative, even though the patient continues to be icteric
- Presence of *urobilinogen*, i.e. *urobilinogenuria* eliminates the possibility of complete biliary tract obstruction, i.e. bile has entered the intestine, where it undergoes enterohepatic metabolism. Urobilinogen appears in the urine in the late preicteric phase of hepatitis, after bilirubinuria. At the height of jaundice, the hepatocytes cannot excrete bilirubin into the bile and hence urobilinogen disappears from the urine. Its reappearance in the urine indicates that the patient is recovering
- Significance of urobilinogenuria and bilirubinuria:

- Hemolytic jaundice: Urobilinogen positive, bile pigment negative;
- Hepatocellular jaundice: Urobilinogen positive (may vary according to phase of disease), bile pigment positive;
- Cholestatic jaundice: Urobilinogen negative, bile pigment positive.

### Serum Bilirubin<sup>†</sup>

- Total bilirubin and bilirubin fractions allow determining whether the cause is due to excess production (i.e. indirect/unconjugate predominant) or impaired conjugation (i.e. direct/conjugated predominant)
- If the conjugated fraction is more than 50% of the total, patient has conjugated hyperbilirubinemia; if the unconjugated fraction is more than 90%, the patient has unconjugated hyperbilirubinemia.

### Serum Albumin

- It is a good indicator of hepatic functional reserve, but because of its long half-life (20-25 days), changes are slow in reflecting liver damage.

### Prothrombin Time (PT)

- Since the activity of coagulation factor prothrombin is dependent on its synthesis by the liver, its estimation, i.e. PT is helpful in assessing the extent of damage in acute liver diseases and their prognosis
- Determination of PT (Quick test) or partial thromboplastin time (PTT) is generally sufficient
- PT is prolonged in hepatocellular etiologies and chronic liver disease
- PTT can be prolonged in vitamin K deficiency (e.g. in obstructive jaundice). In this case, PTT

<sup>†</sup>When considered individually, none of the test analytes in the LFT profile are biologically specific to liver tissues. However, when considered collectively, certain patterns of LFT abnormalities are suggestive of particular sub-groups of hepatobiliary pathologies.

normalizes within 12-24 hours after IV administration of 5-10 mg vitamin K. Absence of normalization indicates serious hepato-cellular damage (e.g. fulminant hepatitis or liver cirrhosis).

### Hepatic Transaminase Enzymes

- Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) are the two enzymes which are sensitive indicators of parenchymal cell integrity
- Although both transaminase enzymes are widely distributed in the body, ALT is predominantly confined to the liver, and therefore, more specific for liver disease. Both tests are sensitive indicators of hepatocellular necrosis
- In general AST is more specific for chronic liver disease and ALT for acute liver disease
- In acute hepatitis, the transaminases are 10 times above normal. In cholestatic jaundice, they are about 5 times above normal. Very high levels may be seen in drug-induced hepatitis, especially paracetamol
- The HCV infection can also produce wide fluctuations in transaminases enzymes, ranging from normal to three to four times the normal range. This *yo-yo phenomenon* is a distinguishing characteristic of HCV infection; therefore, the patient must undergo serial testing for monitoring three to four times yearly throughout his or her lifetime
- A sudden fall in the transaminases in a sick jaundiced patient is indicative of a bad prognosis, as it is seen in acute fulminant hepatitis.

### Serum Alkaline Phosphatase (SAP)

- Useful in detecting early intra- or extrahepatic obstruction; high values (5 times normal) favor obstruction, and a normal SAP virtually excludes this diagnosis.

### Acute Viral Hepatitis Serology Markers (A, B, C and D)

- Generally the following viral hepatitis serology markers are tested:
  - IgM anti-hepatitis A virus—(anti-HAV).
  - IgM anti-hepatitis B core antigen—(anti-HBcAg).
  - Hepatitis B surface antigen—(HBsAg).
  - Anti-hepatitis C virus antibodies—(Anti-HCV; may need PCR for HCV-RNA).
- If HBsAg is present, testing for coexisting HDV by anti-HDV is appropriate<sup>†</sup>
- For the diagnosis of presumed *chronic viral hepatitis*, HBsAg and Anti-HCV serology, using an approved enzyme immunoassay (third generation, i.e. EIA-3), is the initial step. Again, testing for HDV is appropriate if HBsAg is present
- Acute HEV infection can be diagnosed by the presence of IgM anti-HEV and, later in the course, finding of IgG anti-HEV
- The interpretations of viral markers for acute hepatitis A, B, and C, and chronic hepatitis are summarized in Tables 29.2 to 29.4.

### Ultrasound (US)

- This is the most important noninvasive investigation in the evaluation of obstructive (cholestatic) jaundice, e.g. gallstones and choledochal cysts, by detecting dilated bile ducts. False-negatives are generally due to inability to visualize the biliary tree, often due to interposed bowel gas
- It also detects focal liver and pancreas diseases like tumors, abscesses and cysts, (more than 2cm in diameter). It can identify generalized parenchymal disorders like cirrhosis and fatty change. It is also of great help in diagnosing small quantities of ascites.

<sup>†</sup>Hepatitis D can only exist in the presence of hepatitis B, because it requires hepatitis B enzymes to replicate.

**Table 29.2:** Definitions of viral hepatitis serology markers

*HAV*: Hepatitis A virus, the infectious agent that causes HAV infection and hepatitis A.

*Anti-HAV*: Total antibody to hepatitis A virus (HAV) detected in serum of persons with acute or resolved HAV infection; indicates a protective immune response to infection, vaccination, and passively acquired antibody.

*IgM anti-HAV*: Immunoglobulin M antibody to HAV; positive test indicates acute HAV infection.

*HBV*: Hepatitis B virus, the infectious agent that causes HBV infection, hepatitis B, and chronic liver disease.

*HBsAg*: Hepatitis B surface antigen; initial screening test; positive test indicates an active HBV infection; its presence for more than six months in serum defines chronic infection.

*IgM anti-HBc*: Immunoglobulin M antibody to hepatitis B core antigen; positive test indicates acute HBV infection.

*Anti-HBc*: Antibody to hepatitis B core antigen; fractional into IgM and IgG components, i.e. IgM-anti-HBc and IgG-anti-HBc. IgM usually indicates acute infection (in the previous six months); IgG indicates more distant infection that may have been cleared by the immune system, or may persist, in which case +ve HBsAg, and +ve anti-HBc IgG confirm persistent chronic HBV infection.

*HBeAg*: Hepatitis Be antigen; positive test correlates with HBV replication and high infectivity; often called "marker of infectivity".

*Anti-HBs*: Hepatitis B surface antibody; positive test indicates immunity from hepatitis B vaccination (if antibody concentration >10 milli IU/ml).

*HBV/DNA*: Deoxyribonucleic acid from HBV; positive test indicates active replication; useful in monitoring response to treatment of HBV infection (by PCR-based assay).

*Precore mutant*: Term used for patients who are hepatitis B positive (more than 105 copies/ml) and hepatitis Be antigen negative.

*YMDD mutant*: Term used for patients on lamivudine therapy who become hepatitis B DNA negative initially and DNA positive subsequently.

*HCV*: Hepatitis C virus, the infectious agent that causes HCV infection, hepatitis C, and chronic liver disease.

*Anti-HCV*: Antibody to HCV; positive test indicates past or current infection with HCV.

*HCV/RNA*: Ribonucleic acid from HCV; positive test indicates active infection.

*HDV*: Hepatitis D virus, a viroid (incomplete virus) that requires an active (acute or chronic) HBV infection to replicate and cause delta hepatitis virus infection, delta hepatitis, and chronic liver disease.

**Table 29.3:** Initial serologic markers for acute viral hepatitis

VIRUS	Marker	Status
HAV	IgM anti-HAV +ve	Acute hepatitis A
HBV	HBsAg +ve	Acute or chronic hepatitis B*
HCV	Anti-HCV +ve	Acute or chronic hepatitis C
?Viral hepatitis other than A, B and C hepatitis	HBsAg (-ve), Anti-HBc-IgM + IgG (-ve), IgM anti-HAV (-ve), Anti-HCV (-ve)	Rule out CMV, EBV, HZV, HSV; drug/alcohol toxicity; sepsis; and incubating viral hepatitis (i.e. before appearance of antigens)

\*If positive, order test for IgM anti-HBc. (i.e. hepatitis B core IgM antibody; positive result indicate acute HBV infection)

**Table 29.4:** Serologic markers for chronic hepatitis based on etiology

Type of hepatitis	HBsAg	Anti-HCV/HCV/RNA	Anti-HDV/HDV/RNA	Autoantibodies
B	+	–	–	–
C	–	+	–	2-10% anti-LMK1
D	+	–	+	10-20% anti-LMK 3
Autoimmune hepatitis	–	May be +	–	ANA, possibly + ASMA, LMA, LKM 1, etc.



- Duplex sonography is particularly helpful in the diagnosis of portal hypertension, portal vein thrombosis, and other venoocclusive diseases, e.g. Budd-Chiari syndrome.

## INVESTIGATIONS—SPECIFIC

### Serum Amylase

- Elevated in chronic liver disease and extrahepatic obstruction, e.g. pancreatic or common bile duct obstruction by stone or carcinoma.

### HIV Serology

- Indicated in patients with risk factors (*vide clinical notes*).

### CT Scanning

- CT scan is preferred where technical limitations make ultrasound difficult to interpret. It detects smaller focal lesions in the liver, especially when combined with contrast injections, and is useful for differentiating liver lesions (abscess, hepatoma, metastases, hemangioma, and adenoma).

### Endoscopic Retrograde Cholangiopancreatography (ERCP)

- This procedure is used in patients with a high likelihood of extrahepatic obstruction; it allows therapeutic interventions such as stone extraction, and stent placement.

### Magnetic Resonance Cholangiopancreatography (MRCP)

- MRCP is indicated for patients with history of contrast allergy, and patients with altered anatomy, i.e. secondary to surgical procedures or congenital abnormalities; but it does not allow therapeutic interventions as in ERCP.

### X-ray

- An upper GI series may assist in finding a primary neoplasm in the GI tract.

### Antimitochondrial Antibodies

- Present in 85% of patients with primary biliary cirrhosis. Although not specific for this disease, absence of this antibody is strong evidence against the diagnosis of primary biliary cirrhosis.

### Autoantibody Tests

- Autoimmune hepatitis is characterized by positive test results for ANA, antismooth muscle antibodies (ASMA), antibodies to liver/kidney microsomes (LKM), liver cell membrane antibodies (LMA), etc.

### Serum Copper/Ceruloplasmin

- Reduced in Wilson's disease; most patients have a low ceruloplasmin level and low serum copper, and high urinary copper concentrations.

### Serum Iron

- Elevated in hemochromatosis due to secondary causes that are associated with jaundice such as chronic hemolytic anemias, alcoholic liver disease, cirrhosis of liver, and hepatocellular carcinoma.

### Leptospirosis

- ELISA to detect IgM for leptospirosis may be positive in 4-6 days; or PCR—most specific and sensitive for diagnosis in early stages.

### Coombs' Test

- May be done in patients with unconjugated hyperbilirubinemia or hemolytic anemia.

### Liver Biopsy

- Laparoscopy or US-guided liver biopsy is important to diagnose, grade, and stage a mass in the liver, autoimmune hepatitis, hepatic cirrhosis/fibrosis, HCV infection, hemochromatosis, congenital disorders, e.g. Wilson's disease, and to evaluate abnormal or inconclusive biochemical or serological tests.

## CLINICAL NOTES

- Look for the presence of *scleral icterus* as this is a vital clue in distinguishing jaundice from other conditions which impart yellow/brown color to the skin (which is not bilirubin), but the sclerae are spared, e.g. *carotenemia*<sup>§</sup>, *lycopenemia*<sup>\*\*</sup>, hypothyroidism, pernicious anemia, nephrotic syndrome, xanthomata, hemochromatosis, Addison's disease, paraneoplastic syndromes, and drugs such as rifamycin, amiodarone, and mepacrine
- History should always seek to evaluate *risk factors* for hepatitis A, B, and C such as:
  - Travel from endemic areas (hepatitis A and E).
  - Substance abuse—alcohol, anabolic steroids, IV drugs.
  - Viral exposures (hepatitis B and C)—illegal IV drug users, unsafe injection practice, users of intranasal cocaine, accidental needle-stick injury from a person with hepatitis B/C, sexual promiscuity, blood transfusion/receiving clotting factors / transplant (especially before 1992), dental extraction, kidney dialysis, acupuncture, tattooing, body piercing, health care workers in high-risk areas (e.g. dialysis units), and birth to an HBV/HCV-infected mother.
- Drug history—Especially antitubercular, anti-leprosy, and antipsychotic drugs may give a clue about the cause of jaundice
- Family history helps in the diagnosis of classic genetic diseases such as Gilbert's disease (vide *infra* ↓↓) or Wilson's disease, hemochromatosis, and  $\alpha_1$ -antitrypsin deficiency. When liver functions show only an

elevated (>80%) indirect bilirubin level, Gilbert's disease or hemolytic anemia is suggested; whereas direct hyperbilirubinemia (>50%) suggests Dubin-Johnson syndrome. A normal urine urobilinogen will make Gilbert's disease even more likely. Autoimmune hepatitis has a strong genetic predisposition. Besides a variety of autoimmune disorders can be associated with autoimmune hepatitis, e.g. RA, thyroiditis, Graves' disease, ulcerative colitis, vitiligo, etc

- Is the jaundice acute or chronic? Acute onset of jaundice suggests HAV infection, cholangitis, acute biliary tract obstruction, or acute liver failure. Gradual onset of jaundice points to alcoholic liver disease, chronic liver disease (e.g. HBV/HCV infection, chronic active/persistent hepatitis, autoimmune hepatitis), liver failure, or malignancy. A lifelong history of jaundice suggests an inherited metabolic or hemolytic cause
- A patient with classical *Charcot's triad* of upper abdominal pain, fever with chills, and jaundice should be regarded as having ascending cholangitis until proved otherwise
- A patient with anemia and jaundice with no noticeable change in the appearance of the urine and stools is suggestive of hemolytic jaundice
- Is the gallbladder enlarged? The finding of an enlarged gallbladder with jaundice suggests obstructive jaundice due to neoplasm, such as carcinoma of the pancreas, carcinoma of the bile ducts, or ampulla of Vater (*Courvoisier's law*)<sup>††</sup>.

<sup>§</sup>Jaundice is not to be confused with *carotenemia* in which skin turns yellow/orange from *carotene* deposits but the sclerae remain normal in appearance.

<sup>\*\*</sup>*Lycopenemia* is orange-yellow skin discoloration due to the ingestion of large amounts of tomatoes.

<sup>††</sup> *Courvoisier's law* states that, in the presence of jaundice, an enlarged gallbladder is unlikely to be due to gallstones; rather carcinoma of the pancreas or the lower biliary tree is more likely. This may be explained by the observation that the gallbladder with stones is usually chronically fibrosed and so, incapable of enlargement. The converse of Courvoisier's law is not true; the cause of jaundice in a patient with a non-palpable gallbladder is not necessarily gallstones as 50% of dilated gallbladders are impalpable.

- Identify stigmata of chronic liver disease such as spider angiomas, palmar erythema, gynecomastia, and testicular atrophy
- Identify signs of portal hypertension such as dilated collateral abdominal veins, splenomegaly, and ascites; and coagulopathy, e.g. bruising, bleeding, and petechiae
- Presence of a greenish-brown corneal deposit of copper (*Kayser-Fleischer ring*), which is often discernible only with a slit lamp is suggestive of Wilson's disease
- Imaging studies play a limited role, except in suspected cases of malignancy or biliary obstruction
- Because clinical signs are of little or no help for identifying various causes of viral hepatitis, accurate diagnosis can only be achieved with serologic and molecular testing (Table 29.5). Knowledge of the strengths and limitations of these tests allows rational use and interpretation of results.<sup>3</sup>

## RED FLAGS

- HCV infection (*vide infra* ↓↓) must be ruled out in an otherwise asymptomatic patient with persistently elevated ALT
- All drugs, including herbal remedies and illegal drugs, should be suspected as potential hepatotoxins. Iatrogenic (drug) jaundice is more dangerous than viral hepatitis. This is because, if the diagnosis of drug induced hepatitis is missed and the drug is continued, the patient can die
- All patients with HIV infection should be screened for viral hepatitis markers as coinfection of HCV, HBV, and HIV is common due to shared modes of transmission. These coinfections accelerate the course of chronic liver disease and facilitate progression to cirrhosis and hepatocellular carcinoma<sup>4, 5</sup>
- In a jaundiced patient, signs of liver failure, such as encephalopathy, coagulopathy, GI

bleed, ascites, and renal failure indicate severe fulminant acute hepatitis

- Beware of asymptomatic jaundice, especially in an elderly, as neoplasm—primary or metastatic—is a common etiology.

## SELECTIVE GLOSSARY

**Gilbert disease**—It is a chronic, benign, intermittent, and familial (autosomal recessive) condition, occurs predominately in men, characterized by intermittent jaundice in the absence of hemolysis or underlying liver disease. Also known as *unconjugated benign bilirubinemia* and *familial nonhemolytic jaundice*, the unconjugated hyperbilirubinemia in Gilbert syndrome has been recognized as due to underactivity of the conjugating enzyme system bilirubin - uridine diphosphate glucuronyl transferase (UGT-1)—the enzyme that conjugates bilirubin with glucuronic acid. The hyperbilirubinemia is mild and, by definition, less than 6 mg/dl. However, most patients exhibit levels of less than 3 mg/dl. Patients may report vague abdominal discomfort and general fatigue for which no cause is found. Gilbert syndrome is usually diagnosed around puberty, possibly because of the inhibition of bilirubin glucuronidation by endogenous steroid hormones. In older persons, the diagnosis is usually made when unconjugated hyperbilirubinemia is noted on routine blood test results or unmasked by an intercurrent illness or stress. LFTs: with the exception of unconjugated hyperbilirubinemia, standard liver function test results are normal. A diagnosis of Gilbert syndrome can be made in the presence of (1) unconjugated hyperbilirubinemia noted on several occasions; (2) normal results from CBC count, reticulocyte count, and blood smear; (3) normal liver function test results; and (4) an absence of other disease processes or causes of unconjugated hyperbilirubinemia. A simple and easily available

**Table 29.5:** Hepatitis viruses: Interpretation of serologic and molecular findings

<i>Virus</i>	<i>Interpretation / status</i>	<i>Diagnostic test (marker)</i>
HAV	<ul style="list-style-type: none"> <li>• Acute infection</li> <li>• Resolved infection and immunity against reinfection; or vaccination response</li> </ul>	<ul style="list-style-type: none"> <li>• Anti-HAV-IgM (+)</li> <li>• Anti-HAV-IgG (+)</li> </ul>
HBV	<ul style="list-style-type: none"> <li>• Acute</li> <li>• Acute or chronic</li> <li>• Chronic active</li> <li>• Chronic persistent</li> <li>• Resolved</li> </ul>	<ul style="list-style-type: none"> <li>• HBcAb IgM (+)</li> <li>• HBsAg (+)</li> <li>• HBsAg (+); HBeAg (+); HBV/DNA (+)</li> <li>• HBsAg (+); HBcAb IgG (+); HBeAb (+); HBeAg (-); HBV/DNA (-)</li> <li>• HBsAg (-); HBc IGM/IgG Ab (+); HBeAb (+); HBs Ab (+); HBeAg (-); HBV/DNA (-)</li> </ul>
HCV	<ul style="list-style-type: none"> <li>• Vaccination response</li> <li>• Acute/active</li> <li>• Resolved</li> </ul>	<ul style="list-style-type: none"> <li>• HBsAg (-); HBsAb-total (+);</li> <li>• Anti-HCV (EIA +); RIBA (+); HCV/RNA (+)</li> <li>• HCV Ab (+); HCV/RNA (-)</li> </ul>
HDV	<ul style="list-style-type: none"> <li>• Acute/active</li> <li>• Chronic</li> </ul>	<ul style="list-style-type: none"> <li>• Anti-HDV IgM (+); HDV/RNA (+)</li> <li>• Anti-HDV-total (+); HDV/RNA (-)</li> </ul>
HEV	<ul style="list-style-type: none"> <li>• Acute</li> <li>• Active</li> </ul>	<ul style="list-style-type: none"> <li>• Anti-HEV IgM (+);</li> <li>• HEV/RNA (+)</li> </ul>

Ab = Antibody; Ag = Antigen; EIA = Enzyme immunoassay; RIBA = Recombinant immunoblot assay.

bedside oral 'rifampin test' <sup>††</sup> is found to be useful to primarily distinguish Gilbert's disease from other causes of unconjugated hyperbilirubinemic disorders.<sup>6</sup> Besides the usual laboratory methods, genetic analyses of the UDP glucuronyl transferase gene can help in the diagnosis. The major importance of establishing this diagnosis is to reassure patients that the disorder is benign and inconsequential, that the prognosis is excellent, and that further investigations are not essential.

**Hepatitis C viral infection**—HCV infection is not usually diagnosed in the acute phase because most patients are initially asymptomatic, and therefore, have not sought medical attention.

(HCV infection has been called a silent epidemic).<sup>7</sup> Besides, because of the long lag time between initial infection and clinically evident liver disease (20-25 years), early diagnosis of HCV infection can be missed or delayed considerably. Production of antibodies against HCV can be delayed by up to 12 weeks, and about a third of infected individuals might not have detectable antibody at the onset of symptoms.<sup>8</sup> Further, if symptoms do occur, the most common complaints such as fatigue, abdominal pain, poor appetite, weight loss, and pruritus are nonspecific; most HCV-infected patients have no hepatic symptoms. However, almost 40% of patients infected with HCV develop at least one extrahepatic manifestation<sup>9</sup> during the course of the disease such as *mixed cryoglobulinemia*, which is marked by skin involvement, marked by rashes, purpura, petechiae, urticaria, or necrotic ulcerations in the lower extremities (i.e. leukocytoclastic vasculitis); rheumatological manifestations such as joint and muscle aches, fibromyalgia; kidney disease such as membranoproliferative

<sup>††</sup> Rifampin increases total serum bilirubin levels in patients with and without Gilbert's syndrome. On *fasting* for 12 to 24 h, an absolute increase of bilirubin to >1.9 mg/dl 2 to 6 h after the administration of 900 mg of rifampin distinguishes patients with Gilbert's syndrome from those without it. In the *nonfasting* state, an increase in total serum bilirubin to >1.5 mg/dl 4 to 6 h after the administration of rifampin distinguishes persons with Gilbert's syndrome from those without it.

glomerulonephritis, nephrotic syndrome; peripheral neuropathy; sicca syndrome (i.e. pseudo-Sjögren syndrome); and lichen planus. Higher rates of non-Hodgkin's lymphoma, thyroiditis, hypothyroidism, and diabetes mellitus have also been observed in patients with HCV infection. These syndromes are important to recognise, as these extra-hepatic syndromes may be the presenting features for which they seek medical attention. Frequently, extrahepatic manifestations are more serious than the hepatic disease itself and present even in patients with persistently normal ALT levels. A distinct and major characteristic of hepatitis C is its tendency to cause chronic liver disease (i.e. cirrhosis, liver failure, and liver cancer) in the majority, in which the liver injury persists for a prolonged period if not for life. Thus, testing for HCV RNA by PCR or transcription-mediated amplification (TMA) is the only reliable test for the diagnosis of acute infection.

Although, the annual incidence of acute HCV has fallen in recent years, primarily because of effective blood screening efforts and increased education on the dangers of needle sharing, hepatitis C infection is still relatively frequent in certain populations. With more than 170 million chronic hepatitis C patients worldwide and an increase in the related morbidity and mortality projected for the next decade, an improvement in our ability to diagnose and treat patients with acute hepatitis C would have a significant impact on the prevalence of chronic hepatitis and its associated complications particularly in countries with a high endemic

background of the infection.<sup>10</sup> It is, therefore, mandatory for the physician to become more aware of the optimal methods for screening, diagnosing, and treating this potentially devastating condition.<sup>11</sup>

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## CHAPTER

# 30

## Myalgia

### SYNOPSIS

*Myalgia*\* may be described as a poorly localized aching in a muscle or group of muscles, usually characterized as a deep aching sensation, but sometimes as a burning or electric sensation. In addition to the origin of myalgic pain in muscle tissue *per se* (i.e. *myopathies*), diseases of subcutaneous tissue, fascia, tendon, bones, joints, and peripheral nerves may also produce pain that is *referred* to muscle.

Myalgia may be classified as:

- *Acute*—Less than a month, e.g. viral fever, minor muscular strain
- *Chronic*—More than 3-6 months, e.g. injury
- *Localized*—involving one or few muscle groups, e.g. compartment syndromes, peripheral vascular disease
- *Generalized*—Involving more than four areas, e.g. drug-induced or toxic myopathies, fibromyalgia, CFS
- *Episodic*—e.g. metabolic myopathies
- *Constant*—e.g. inflammatory myopathies.

\*Myalgia should not be confused with muscle 'weakness', i.e. reduction in muscle power; muscle 'fatigability', i.e. inability to sustain the performance of an activity; or 'cramps', i.e. episodic involuntary contraction of muscles.

Diagnosis begins with patient's history, distinguishing muscle pain from muscle *weakness*, i.e. reduction in muscle power; muscle *fatigability*, i.e. inability to sustain the performance of an activity; or *cramps*, i.e. episodic involuntary contraction of muscles. The pattern and severity of muscular pain, associated symptoms, medication use, and family history are helpful to determine whether the cause of myalgia is a normal reaction to physical exertion or pathological infectious, inflammatory, rheumatologic, endocrine, metabolic, electrolyte-induced, drug-induced, neurogenic, or genetic disorders.

Advances in techniques such as application of molecular genetics, electrophysiology, and muscle biopsy have made a definitive diagnosis possible for many myopathies. However, a phenotypic approach to diagnosis according to the patient's predominant pattern of weakness is essential, which will be useful in selecting the most appropriate diagnostic studies to establish a precise diagnosis, and inform the patient about the nature and evolution of the disease, the therapeutic options, and to propose, when indicated, genetic counseling.<sup>1,2</sup>



## DIFFERENTIAL DIAGNOSIS

### Common

- Muscle overuse syndrome (extreme physical exertion)
- Weekend warrior syndrome<sup>†</sup>
- Delayed onset muscle soreness (DOMS: *vide infra* ↓↓)<sup>3</sup>
- Postinfectious (viral: Dengue, Chikungunya, HIV; bacterial: Influenza; *nematode: Trichinosis: vide infra* ↓↓)
- Localized muscle pain (trauma; mass, e.g. hematoma, neoplasm; fibrositis; tendinitis)
- Psychogenic (depression, anxiety)
- Fibromyalgia<sup>‡</sup>
- Chronic fatigue syndrome (CFS)
- Dehydration (hyponatremia).

### Occasional

- Connective tissue disorders (RA, SLE, PAN, PMR)
- Endocrine myopathies (hypothyroidism, thyrotoxicosis, diabetes mellitus, hyperlipidemia)
- Drug-induced/toxic myopathies<sup>4</sup> (stains: rhabdomyolysis: *vide infra* ↓↓, steroids, alcohol, diuretics, cimetidine, antiretroviral therapy)
- Ischemic myalgia (DVT, intermittent claudication due to occlusive arterial disease).

### Rare

- Infectious myositis (poliomyelitis, rabies, tetanus, Guillain-Barré syndrome, pyomyositis, gas gangrene, Toxoplasma myositis, Cysticercosis, Lyme myositis)
- Inflammatory myopathies (polymyositis, i.e. PM; dermatomyositis, i.e. DM)

- Metabolic bone disease (osteomalacia, hyperparathyroidism)
- Malignancy/ paraneoplastic syndromes
- Porphyria (acute, intermittent)
- Eosinophilic myalgic syndrome (EMS: *vide infra* ↓↓)
- Hereditary myopathies (hypokalemic myopathy, glycogen metabolism disorders).

## INVESTIGATIONS—GENERAL

### CBC

- Eosinophil counts of 10,000-30,000 cells/μl are not unusual in a rare case of EMS.

### ESR

- More than 50 mm/hr. with no other abnormality suggests PMR, though a normal ESR does not rule out this diagnosis.

### Urine

- Myoglobinuria causes red or cocacola colored urine in rhabdomyolysis.

### CPR

- May be elevated prior to ESR.

### CK (with Isoenzymes)

- The CK level may be highly elevated (10 – 100 times normal) in the inflammatory myopathies, and can be moderately to highly elevated in the muscular dystrophies. Other conditions that can be associated with elevated CK levels include infections, alcoholism, and adverse reactions to medications. Metabolic (storage) myopathies tend to be associated with only mild to moderate elevations in CK levels. The CK level usually is normal in the electrolyte and endocrine myopathies (notable exceptions are thyroid and potassium disorder myopathies).

<sup>†</sup>Recreational pursuits with poor conditioning or appropriate training.

<sup>‡</sup>Formerly called as Fibromyositis or Myofascial pain syndrome.

- However, the absence of an elevated serum CK level does not exclude myopathy. In addition, elevation of the serum CK does not necessarily imply that the muscle is the primary site of abnormality.<sup>5,6</sup>
- The serum CK level is the most sensitive for muscle disease, and it is rarely necessary to measure other enzymes that are released from injured skeletal muscles such as AST, ALT, or LDH, all of which are also elevated in hepatic disease.

## INVESTIGATIONS—SPECIFIC

### FBG, PPBG

- May be abnormal before other abnormalities of this disease are manifest.

### Calcium

- Hypercalcemia may be associated with hyperparathyroidism, or metastatic carcinoma.

### Electrolytes

- Hypokalemia is usually diuretic induced.

### Sr Alkaline Phosphate

- Usually elevated in osteomalacia, hyperparathyroidism, metastatic carcinoma, Paget's disease.

### TFTs

- High TSH values may be the only abnormality of hypothyroidism; low TSH values with corresponding high T3 and T4 values confirm thyrotoxicosis.

### ANA, RF

- Likely to be positive in connective tissue disorders; if RF/ANA assay is positive, additional studies such as double-stranded DNA, or antiphospholipid antibodies (lupus) may be obtained.

### X-rays

- May be essential in trauma cases.

### EMG

- Although changes seen on EMG are not pathognomonic for any specific disease process, an abnormal EMG is useful to evaluate the extent and pattern of myopathic process, and to evaluate for a neuropathy or a disease of the neuromuscular junction.

### NCS

- To exclude peripheral neuropathy.

### MRI

- Muscle imaging, in particular MR, provides diagnostic and follow-up information, especially in dystrophic, metabolic, and inflammatory myopathies
- Useful to identify areas of abnormal muscle that are amenable to biopsy.

### Endocrine/Metabolic Panel

- Where indicated, additional tests such as 24-hour urine cortisol testing to rule out Cushing's disease; oral glucose load/growth hormone assay to rule out acromegaly; and vitamin D assay to rule out osteomalacia may be obtained.

### Muscle Biopsy/Genetic Analysis

- If the diagnosis is still inconclusive after the history, physical examination, and laboratory, radiologic, and electromyographic evaluations, a muscle biopsy is required for patients who have a suspected myopathy. The pathologic analysis of biopsy specimens focuses on the histologic, histochemical, electron microscopic, genetic, and biochemical changes that are found in the affected muscle. Molecular analysis of candidate genes is becoming a major diagnostic tool in many muscle disorders.

## CLINICAL NOTES

- It is vital to distinguish myalgia from articular symptoms; if the lesion is in the muscle, the pain is greater during active than passive movement of the affected muscle; if in the ligament or joint, the pain is about equal
- It is also important to differentiate myalgia and myopathies due to disease of nervous system. The presence of muscle wasting<sup>§</sup>, fasciculation, sensory and motor changes, as well as associated neurologic evidence favors neurogenic cause such as due to UMN, LMN, neuromuscular, motor neuron, or peripheral nerve disorder
- Historical aspects which are helpful in the diagnosis include:
  - The age of the patient (myopathies since birth and childhood, as against adult onset—usually acquired myopathies).
  - Recent events surrounding the occurrence of myalgia (e.g. postexercise, new vocational activities, new drug intake).
  - Onset and progression of the disease (see classification above).
  - Preceding history of trauma, febrile illness.
  - Occupation, hobbies (gardening), sports (DOMS), and recreational activities (tennis/golf elbow).
  - Drugs or toxin exposure.
  - Food habits (trichinosis).
  - Psychosocial history.
  - Family history (connective tissue disorders, hereditary myopathies).
- The muscle power should be tested at the bedside by examining all muscle groups bilaterally, which is usually graded as below:
  - Grade – 5: normal power
  - Grade – 4: active movements against gravity and resistance
  - Grade – 3: active movements against gravity
  - Grade – 2: active movements only with gravity eliminated
  - Grade – 1: traces contractions
  - Grade – 0: no contraction.
- Characteristic facies and bone structure of acromegaly suggest myopathy associated with this disease. Lethargy, dry skin and hair, nonpitting edema, a husky voice suggest hypothyroidism
- A rapid onset of myalgia in an elderly female involving the muscles of the neck, shoulder, buttocks and thighs is diagnostic of PMR. The muscles below the elbows and knees are not affected in this condition
- Temporal artery thickening or tenderness and bruits over carotid may be found in few cases of PMR
- A gradual onset of generalized myalgia with multiple tender spots on both sides of the body, above and below the waist is typical of fibromyalgia. The diagnosis of fibromyalgia is clinical. There is no laboratory or imaging tests to confirm this diagnosis
- Myalgia with significant and progressive leg weakness causing difficulty in climbing stairs, squatting, getting into or out of a car, rising from a chair, raising hands above the head, holding head up, combing hair, and lifting objects strongly favor the diagnosis of inflammatory muscle diseases such as PM and DM. In contrast to myasthenia gravis, PM and DM do not cause facial or ocular muscle weakness
- In DM, cutaneous manifestations can precede, follow, or develop together with muscle weakness. Cutaneous findings include rash on the neck (V sign), shoulders, and upper back (shawl sign), a purplish (heliotrope) effusion on the upper eyelids, and scaly patches over the dorsum of proximal and distal interphalangeal joints (knuckles), called *Gotttron's sign*

<sup>§</sup>Muscle wasting which occurs secondary to neurological disease is usually referred to as *amyotrophy*.

- Presence of associated symptoms or signs, indicating involvement of organs or tissues other than muscle, such as dyspnea, orthopnea, respiratory failure, congestive heart failure, arrhythmias, cataracts, mental retardation, and hepatomegaly is valuable in the clinical diagnosis of hereditary myopathies (e.g. myotonic dystrophy, Duchenne's or Becker's muscular dystrophies)
- Normal findings on a battery of investigation do not rule out organic disease, but strongly suggest psychogenic disorders.

### RED FLAGS

- As there is a close relation of PMR with giant cell arteritis (GCA), once the diagnosis of PMR is entertained, it is prudent to question and examine these patients for symptoms and signs of GCA, such as headache, especially in temporal region, scalp tenderness, jaw pain, visual disturbance, tender temporal arteries, and signs of ischemic retinopathy on funduscopic examination. If GCA is suspected, steroid therapy is indicated
- Since there is an increased risk of malignancy in patients with DM and PM, they should be offered age and risk specific cancer screening tests, such as chest/abdomen/pelvis CT, GI tract imaging and mammography. Malignancies may be evident at the time of presentation, but may not be detected until months afterward in some cases.

### SELECTIVE GLOSSARY

**Delayed onset muscle soreness (DOMS)**—It is a sensation of discomfort or soreness that occurs 1 to 2 days after exercise, commonly due to microinjury to the muscle or eccentric activity. It is most evident at the muscle/tendon junction initially, and then spreading throughout the muscle. Symptoms can range from muscle tenderness to severe debilitating pain, usually

involving the quadriceps muscle group, but may also affect the hamstring, and triceps surae groups. Up to six hypothesized theories have been proposed for the mechanism of DOMS, namely: lactic acid, muscle spasm, connective tissue damage, muscle damage, inflammation and the enzyme efflux theories. The mechanisms, treatment strategies, and impact on athletic performance remain uncertain, despite the high incidence of DOMS. Clinically, DOMS is a self-limiting condition that usually requires no treatment.

**Eosinophilia-myalgia syndrome**—The term EMS was coined in 1989 after a cluster of cases with symptoms of incapacitating myalgias and eosinophilia were reported, most commonly in people aged 35-60 years. This syndrome has been only defined as varying degrees of myalgias and peripheral eosinophilia. In November 1989, for the purpose of nationwide surveillance, the US Centers for Disease Control and Prevention (CDC) defined this syndrome according to 3 criteria: (1) a blood eosinophil count greater than 1000 cells/ $\mu$ l, (2) incapacitating myalgia, and (3) no evidence of infection (e.g. trichinosis) or neoplastic conditions that would account for these findings. Studies confirmed a strong association between the use of a specific brand of L-tryptophan and development of EMS; the best characterized of these is 1,1-ethylidenebis (L-tryptophan) (EBT), a tryptophan dimer. However, contaminated L-tryptophan may not be the only cause of EMS. Symptoms other than myalgia include arthralgia, peripheral edema, alopecia, scleroderma-like skin changes, and various GI, pulmonary, and neurological manifestations. Eosinophil counts of 10,000-30,000 cells/ $\mu$ l are not unusual, and the bone marrow shows hyperplasia of eosinophil precursor cells. With the recall of L-tryptophan from the market in November 1989, only a few new cases have been reported.

**Rhabdomyolysis and Myoglobinuria**—It is a disorder characterized by acute damage of the sarcolemma of the skeletal muscle, leading to release of potentially toxic muscle cell components into the circulation, most notably CK and myoglobin, and is frequently accompanied by myoglobinuria. Therefore, the term myoglobinuria is often used interchangeably with the term rhabdomyolysis. *Myoglobinuria* refers to an abnormal pathologic state in which an excessive amount of myoglobin is found in the urine, imparting a cola-like hue, usually in association with myonecrosis, and a clinical picture of weakness, myalgias, and edema. The condition is etiologically heterogeneous and may result from a large variety of diseases affecting muscle membranes, membrane ion channels, and muscle energy supply, including acquired causes (e.g. exertion, crush injury and trauma, alcoholism, drugs, and toxins), and hereditary causes (e.g. disorders of carbohydrate metabolism, disorders of lipid metabolism, or diseases of the muscle associated with malignant hyperthermia).

In many patients with idiopathic recurrent rhabdomyolysis, specific inherited metabolic defects have not been recognized up to now. Acute renal failure is the most serious complication, which can be prevented by prompt, aggressive treatment. In patients surviving acute attacks, recovery of muscle and renal function is usually complete.

**Trichinosis**—It is the result of infection by the nematode *Trichinella spiralis*. Humans are infected incidentally when they eat inadequately cooked meat that contains larvae of *Trichinella* species. Most infestations do not cause symptoms, although heavy exposure can cause various clinical manifestations, including diarrhea, fever, myalgias, and prostration. Factors that may affect morbidity include the

quantity of larvae ingested, the species of *Trichinella* (most notably *T spiralis*), and the immune status of the host. After two weeks, majority of the patients have fever that peaks around the fourth week. Weakness and/or myositis follow; the muscles become stiff, hard, and edematous. Muscles with increased blood flow, e.g. extraocular muscles, masseters, larynx, tongue, neck muscles, diaphragm, intercostals, limb flexors, and lumbar muscles are most frequently involved. Involvement of the diaphragm may result in dyspnea. Other symptoms include: periorbital edema and rash (macular or petechial). CK levels are elevated to >15,000 U/l. Serology results are not positive until 2-3 weeks after infection. They peak around the third month and may persist for years. In patients with CNS involvement, CT scanning and MRI with contrast enhancement may reveal 3- to 8-mm nodular or ring-like lesions. Muscle biopsy provides a definitive diagnosis; however, it is rarely recommended except in difficult cases when serology tests are unhelpful.

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## CHAPTER

# 31

## Nausea and Vomiting

### SYNOPSIS

*Nausea*\* is an unpleasant sensation and an impending desire before vomiting, usually accompanied by autonomic signs such as pallor, hypersalivation, diaphoresis, tachycardia, and tachypnea.

*Vomiting* is a physical event that results in the speedy, forceful evacuation of gastric contents through the mouth which may or may not be preceded by nausea. Vomiting may be a protective physiologic mechanism that prevents entry of potentially harmful substances into the GI tract. However, persistent vomiting can lead to complications such as dehydration, metabolic alkalosis, hyponatremia, hypokalemia, esophagitis, gastritis, aspiration pneumonitis, and rarely Mallory-Weiss syndrome, or Boerhaave syndrome (*vide infra* ↓↓) — irrespective of the cause of vomiting.

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\*According to one Midwestern survey, *nausea* was not understood by two-thirds of medical, surgical, and gynecologic patients queried. The expression *sick at stomach*, on the other hand, was the most common patient descriptor of *nausea*, and the expression *throw up* was consistently interpreted as *vomiting*.- Ref. RhodesVA et al. **Nausea, Vomiting, and Retching: Complex Problems in Palliative Care.**CA Cancer J Clin 2001 51: 32-248. [PMID: 11577489: Free full text].

It is important to differentiate vomiting from other physical phenomenon such as regurgitation, rumination, and retching.

*Regurgitation* is a passive phenomenon indicating an effortless reflux of gastric contents into the mouth, which may be due to mechanical obstruction of the esophagus, GERD, or esophageal motility disorders.

*Rumination* is also a passive phenomenon, during which recently ingested food is regurgitated effortlessly into the mouth, whereupon it is re-chewed and swallowed or spat out.

*Retching* (spasmodic respiratory and abdominal movements) is a strong involuntary effort to vomit, but occurs against a closed glottis, without bringing up emesis.

Although nausea and vomiting are common complaints<sup>†</sup>, they are usually self-limiting and benign in nature. However, they may occasionally herald serious etiologies. Hence careful assessment is required; together with a willingness to review and admit the patient if the diagnosis remains unclear.

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<sup>†</sup> Though nausea and vomiting may occur independently, they are so closely related - produced by the same stimuli and can be viewed as a progressive response to increased stimulus - that they are considered together.



The American Gastroenterological Association suggests a 3-step approach to the initial evaluation of nausea and vomiting:<sup>1</sup>

- Recognize and correct any consequences of the symptoms, such as dehydration or electrolyte abnormalities
- Try to identify the underlying cause and provide specific therapy
- Use empiric therapy if no cause can be found.

## DIFFERENTIAL DIAGNOSIS

### Common

#### GI Disorders

- Gastritis (*H. pylori* infection; aspirin; NSAID; other drugs, e.g. oral steroids; excess alcohol; stress; viral infections)
- Acute infections (gastroenteritis, food poisoning)
- Inflammation (appendicitis, peptic ulcer disease, viral hepatitis)
- Motility disorder (GERD)
- Colic (renal, biliary)
- Functional (NUD)

*Systemic infections* (febrile illness; RTI; UTI; Septicemia)

*Cardiac ischemia* (MI: especially inferior/posterior wall; CHF)

*CNS disorders* (migraine; CVD: infarction, hemorrhage; Infection: meningitis-viral, bacterial, TB; raised ICP: abscess, hematoma, and tumor)

*Labyrinthine disorders* (Motion sickness, Ménière's disease, and Vestibular neuronitis)

*Pregnancy* (hyperemesis gravidarum, ectopic pregnancy)

*Postoperative* (Paralytic ileus).

### Occasional

#### GI Disorders

- Inflammation (cholecystitis, pancreatitis, peritonitis)

- Obstruction (achalasia, pyloric stenosis, small/large bowel obstruction, strangulated hernia, volvulus).

*Metabolic* (DKA, gastroparesis: *vide infra* ↓↓, hypertensive encephalopathy, uremia, electrolyte imbalance).

*Ophthalmic* (acute closed-angle glaucoma).

*Opportunistic infections* (candida esophagitis, CMV or HSV infection in AIDS).

### Rare

- Torsion (testicular, ovarian)
- Malignancy (esophagogastricduodenal/pancreatic carcinoma, hepatoma, metastasis, paraneoplastic syndrome: *vide infra* ↓↓)
- Ischemia (mesenteric)
- Metabolic (hypercalcemia, renal tubular acidosis)
- Endocrine (hyperparathyroidism, adrenal crisis: *vide infra* ↓↓)
- Poisoning (organophosphate compounds)
- Hematologic (acute intermittent porphyria: *vide infra* ↓↓)
- Psychogenic (bulimia nervosa, sitophobia, conversion disorders)
- Cyclic vomiting syndrome (*vide infra* ↓↓).

## INVESTIGATIONS—GENERAL

### CBC

- Leukocytosis in inflammation; microcytic anemia due to occult blood loss and malignancy.

### ESR

- Elevated in inflammatory and malignant disease.

### Urea, Creatinine, Electrolytes

- Severe or protracted vomiting of gastric contents may lead to hypokalemia, uremia, or metabolic alkalosis or acidosis.
- Hyponatremia or hyperkalemia (or both) is commonly seen in adrenal crisis.

**LFTs, Amylase, Lipase**

- Elevated in pancreaticobiliary disease.

**CXR**

- Pneumonia, bronchitis, CHF, malignancy may trigger vomiting.

**AXR**

- Supine and upright AXRs are obtained in patients with severe pain or suspicion of bowel obstruction, perforation, or ileus — to look for dilated loops of small bowel or pneumoperitoneum.

**ECG**

- To rule out myocardial ischemia, infarction.

**Blood Glucose**

- Elevated in DKA; low in adrenal crisis.

**Serum Calcium**

- Elevated in hyperparathyroidism, malignancy, and adrenal crisis.

**Urine**

- Ketones in DKA; porphobilinogen in porphyria.

**Pregnancy Test**

- Urine hCG test for any women of child-bearing age.

**INVESTIGATIONS—SPECIFIC****US Abdomen and Pelvis**

- Helpful in patients with gallbladder (cholecystitis, cholelithiasis), hepatic (hepatitis, cirrhosis), and pancreatic disease (pancreatitis, carcinoma); may reveal urolithiasis,

organomegaly, and mass lesion causing mechanical bowel obstruction.

**Endoscopy** (i.e. EGD/Sigmoidoscopy/Colonoscopy).

- To evaluate mucosal lesions (ulcers, malignancy), and to obtain biopsy specimens.

**HRCT Abdomen**

- To evaluate for abdominal mass or obstruction.

**CT Scan/MRI Head**

- In patients with suspected CNS cause or with abnormal neurologic signs such as altered consciousness and papilledema.

**Upper GI/Barium Enema X-rays**

- With barium contrast and follow-through — to detect mucosal lesions (ulcers), obstruction, or mass lesion.

**Nuclear Scintigraphy**

- Gastric emptying scintigraphic studies to confirm gastroparesis.

**Audiometry**

- Useful in patients with Ménière's disease, labyrinthine disease.

**Toxicology Screen**

- To evaluate serum levels of drug effect, e.g. digoxin, theophylline, anticonvulsants or toxins, e.g. pesticides, insecticides causing vomiting.

**CLINICAL NOTES**

- The foremost aspect in history taking and examination is an attempt to recognize and correct any consequences of nausea and vomiting such as dehydration or electrolyte abnormalities, regardless of the underlying cause (Table 31.1)
- Warning signs such as fever, hypotension, severe dehydration, chest pain, severe

**Table 31.1:** Key questions in the evaluation of acute nausea and vomiting

1. Immediate therapy (for intravascular volume depletion) —Is it needed regardless of the cause?
2. Are symptomatic treatment and reassurance sufficient?  
For example:  
In patients with symptoms consistent with a —
  - Viral syndrome
  - Motion sickness
  - Food intolerance
  - Emotional-stressful event
3. Is urgent workup needed to establish the cause?  
For example:
  - In a pregnant woman
  - Evidence of systemic disease
  - Presence of chest pain
  - Presence of CNS symptoms
  - History of drug / alcohol abuse or toxin exposure
  - An immunocompromised patient
  - Postoperative status

abdominal pain, CNS symptoms, history of immunosuppression, or older age should prompt immediate evaluation and treatment

- Evaluation of vital signs (fever, pulse, and blood pressure to assess hydration, and respiratory rate to look for acidosis-related hyperventilation); skin, eyes, mucous membranes (dehydration, jaundice); and signs of systemic disease e.g. tachycardia, S<sub>3</sub> gallop, pedal edema with CHF, are areas of key importance

- Acute nausea and vomiting, i.e. symptoms present for less than a week, is most often due to GI infection, inflammation, obstruction; systemic illness; drug toxicity; alcoholism; labyrinthine disorders; and occasionally psychogenic conditions
- Chronic nausea and vomiting, i.e. presence of symptoms over a week, may be due to a number of different conditions; the patient may describe intermittent symptoms lasting months or years. The common causes include gastritis, mechanical obstruction, gut motility disorders (including diabetic gastroparesis), drugs, labyrinthine disorders, and uremia. A thorough history and physical examination

are invaluable in pointing to the correct diagnosis

- The precise features of vomiting, and its temporal relationship to food intake generally provide a clue to the diagnosis (Table 31.2).

**Table 31.2:** Vomiting—clinical correlation

Features of vomiting	Possible causes
<ul style="list-style-type: none"> <li>• Early morning hours, before eating</li> <li>• Shortly after eating</li> <li>• Delayed vomiting</li> <li>• No clear relationship to meals</li> <li>• Vertigo, tinnitus</li> <li>• “Projectile”, unaccompanied by nausea</li> <li>– “Bilious”</li> <li>– “Putrid”</li> <li>– “Feculent”</li> <li>gastrocolic fistula</li> <li>• Only symptom for years</li> </ul>	<ul style="list-style-type: none"> <li>• Pregnancy (first trimester), alcohol abuse, depression, increases ICP, uremia</li> <li>• Esophageal disease, gastritis, ulcer disease, gastric outlet obstruction, gastroparesis, gastric carcinoma, psychogenic</li> <li>• Intestinal obstruction</li> <li>• Metabolic disorders, drugs, toxins,</li> <li>• Labyrinthine disease</li> <li>• Increased ICP</li> <li>– Postoperative</li> <li>– Gastric outlet obstruction</li> <li>– Intestinal obstruction,</li> <li>• Psychogenic</li> </ul>

- Associated symptoms such as fever, headache, and myalgia (viral); severe abdominal pain (obstruction); weight loss, hematemesis, melena (ulcer, malignancy, Mallory-Weiss tear); jaundice (hepatitis, hepatoma, and extrahepatic causes); diarrhea (gastroenteritis); vertigo (labyrinthine disorders); photophobia (migraine); and drug ingestion may suggest the cause of underlying disease
- History of peptic ulcer is an indicator of further ulceration, while patients with *functional* dyspepsia tend to be depressed or anxious, and tend to exhibit somatization, characterized by multiple symptoms and frequent consultations
- An inquiry into patient’s psychological and social history, and of symptoms that may indicate a psychological disorder is important. *Psychogenic* vomiting is characterized by a

combination of features such as a lengthy history of vomiting, superstitious vomiting, often self-induced, evidence of psychological disorders (anxiety, depression), and maintenance of normal health despite long-standing vomiting

- Though nausea and vomiting associated with pronounced weight loss (>3 kg) seemingly indicates serious disorders such as obstruction, malignancy, or mesenteric ischemia, it is common in functional or psychogenic dyspepsia due to *sitophobia*<sup>†</sup>, i.e. an aversion to food or refusal to take nourishment
- Physical signs of pregnancy, alcoholism, abdominal mass, peritonitis, obstruction, neurological signs (altered mental state, neck stiffness, papilledema, and nystagmus), ear examination (middle ear disease), ophthalmic and funduscopic examination (raised ICP, glaucoma), generally indicate the underlying diagnosis
- A distended abdomen associated with nausea and vomiting may indicate paralytic ileus or mechanical obstruction of the intestine. Abdominal tenderness, distension, and occasionally visible peristalsis suggest GI obstruction. A succussion splash suggests diabetic gastroparesis.

## RED FLAGS

- Acute nausea and vomiting may subside within days, only to recur later to present a chronic disorder, posing a more challenging diagnostic dilemma
- Persistent vomiting with hypercalcemia may be the initial presentation of asymptomatic hyperparathyroidism, underlying neoplasm or paraneoplastic syndrome
- In an intoxicated alcoholic patient with nausea and vomiting-acute pancreatitis and

intracranial hemorrhage (subdural hematoma, intracerebral bleeding, or contusion) must be ruled out.

## SELECTIVE GLOSSARY

**Acute intermittent porphyria**—It is inherited as an autosomal dominant pattern, caused by partial deficiency of porphobilinogen deaminase activity, leading to increased excretion of aminolevulinic acid and porphobilinogen in the urine. It remains clinically silent in the majority, but may manifest, usually in women beginning in the teens or 20s. Clinical features include intermittent abdominal pain (may mimic acute abdomen), vomiting, and neurologic manifestations such as seizures, muscle pain, tingling, numbness, weakness, paralysis, and psychosis. Attacks are precipitated by numerous factors, including drugs and intercurrent infections. In contrast to other forms of porphyria, cutaneous hypersensitivity is absent in acute intermittent porphyria. Diagnosis can be confirmed by demonstrating increased amount of porphobilinogen in the urine during an acute attack.

**Adrenal crisis**—It is characterized by profound asthenia, severe pain in the abdomen, muscle cramps, nausea, vomiting, diarrhea, peripheral vascular collapse, and finally, renal shutdown with azotemia. Body temperature may be low, although severe fever often occurs, particularly when crisis is precipitated by acute infection. Adrenal crisis may result from an acute exacerbation of chronic insufficiency, usually caused by sepsis or surgical stress, adrenal hemorrhage (e.g. Waterhouse-Friderichsen syndrome [fulminant meningococcemia]) and anticoagulation complications. Steroid withdrawal is the most common cause of adrenocortical insufficiency, and it almost exclusively causes a glucocorticoid deficiency. Sometimes, the diagnosis is considered only on discovery of characteristic abnormalities of serum electrolytes,

<sup>†</sup> Other terms used for 'food' phobia include 'phagophobia', i.e. fear of eating and 'cibophobia', i.e. fear of food.

including low Na (<135 mEq/l), high K (>5 mEq/l), low  $\text{HCO}_3^-$  (<15 to 20 mEq/l), and high BUN (>20 mg/dl). A high index of suspicion is therefore required in patients with unexplained fatigue, hyponatremia or hypotension.

**Boerhaave syndrome (Pronunciation: buˈrˈhah-veˈ)**—It denotes esophageal perforation or rupture of the esophagus caused by increased intraluminal pressure and distension during retching or vomiting. The presence of a hole or other type of opening in the esophageal wall facilitates the passage of esophageal contents into the mediastinum resulting in mediastinitis. The most common cause of esophageal perforation is injury during a medical procedure such as esophagoscopy or placement of a nasogastric tube, and pathologic process such as neoplasm or gastric reflux with ulceration. Less common causes include injuries from penetrating or blunt trauma or injury to the esophagus during an operation on another organ, mechanical problem such as violent retching or vomiting; ingestion of a foreign body or caustic agents. The condition often results in infection of the mediastinum and mediastinitis. The *Mackler triad* is the classic presentation of spontaneous esophageal rupture is in a middle-aged man with a history of *recent vomiting or retching after dietary overindulgence and overconsumption of alcohol, with chest pain and subcutaneous emphysema*.

**Cyclic vomiting syndrome**—CVS causes bouts or cycles of severe nausea and vomiting that last for hours or even days, and alternate with longer periods of no symptoms. The disorder which has no known cause typically begins between the ages of 3 and 7 years. Children tend to outgrow CVS when they are teenagers. While the disorder occurs most often in children, CVS can begin at any age. Adult episodes tend to occur less often than they do in children, but they usually last longer. Furthermore, the events or situations that trigger episodes in adults such as coryza,

sinusitis, emotional stress, excitement, physical exhaustion, foods such as chocolate or cheese, menstruation, hot weather etc. cannot always be pinpointed as easily as they can in children. Each episode is similar to the previous ones. The episodes tend to start at about the same time of day, last the same length of time, and present the same symptoms at the same level of intensity. CVS appears to be linked to migraines in some cases. Treatment with migraine medications often helps. Because other more common diseases and disorders also cause cycles of vomiting, many people with CVS are initially misdiagnosed until the other disorders can be ruled out. To be diagnosed with CVS, a person must have experienced at least two episodes of intense nausea and unremitting vomiting or retching lasting hours or days. These episodes must be separated by weeks or months of symptom-free intervals. There is no specific test that will confirm the diagnosis of CVS. Other conditions that can produce vomiting, such as, labyrinthine disease, metabolic disorders, CNS tumors, and pregnancy must be excluded.

**Gastroparesis**—Literally translated, it means *stomach paralysis*—is a digestive disorder in which the motility of the stomach is either abnormal or absent. Normally, the stomach contracts to move food down into the small intestine for digestion. The vagus nerve controls the movement of food from the stomach through the digestive tract. Gastroparesis occurs when the vagus nerve is damaged, and the muscles of the stomach and intestines do not work normally. Food then moves slowly or stops moving through the digestive tract (delayed gastric emptying). The most common cause of gastroparesis is diabetes mellitus; other causes include hypothyroidism, vagotomy, gastric bypass surgery, viral infections, medications such as anticholinergics and narcotics, smooth muscle disorders such as amyloidosis and scleroderma;



Parkinson's disease; multiple sclerosis; and idiopathic gastroparesis. Signs and symptoms of gastroparesis are: heartburn, pain in the upper abdomen, nausea, vomiting of undigested food—sometimes several hours after a meal; early feeling of fullness after only a few bites of food; weight loss due to malnutrition; abdominal bloating, lack of appetite, and gastroesophageal reflux. Gastric emptying scintigraphy of a radiolabeled solid meal for 2 hours confirms the diagnosis of gastroparesis. Performing the test for a longer duration, up to 4 hours, has been proposed to increase the yield in detecting delayed gastric emptying in symptomatic patients.

**Paraneoplastic syndromes**—PNS can be defined as a group of symptoms that may develop due to indirect and usually remote immune-mediated effects produced by tumor cell metabolites or other products which disrupt the normal function of surrounding cells and tissue. Body systems that may be affected by PNS include neurological, endocrine, cutaneous, renal, hematologic, gastrointestinal, and other systems. The most common manifestations of PNS are cutaneous, neurologic, and endocrine disorders. An example of a cutaneous paraneop-

lastic disorder is telangiectasis, which can be caused by breast cancer and lymphomas. Lambert-Eaton myasthenic syndrome is a neurologic PNS that can be caused by a variety of tumors including small cell lung cancer, lymphoma, breast, colon and other cancers. Syndrome of inappropriate antidiuretic hormone (SIADH) is an endocrine PNS, which is seen in as many as 40% of patients diagnosed with small cell lung cancer. Symptoms generally develop (depending on body system affected) over a period of days to weeks and usually occur prior to tumor detection, which can complicate diagnosis. Some paraneoplastic syndromes may be confused with metastatic disease or spread of the cancer. The presence of the syndrome may be the only indication that a patient has a malignancy or that a malignancy has recurred. Specific diagnosis depends on demonstration of specific autoantibodies in various tissues of the body and imaging studies such as MRI, PET, and SPECT scans.

## REFERENCE

1. Quigley EM, et al. AGA technical review on nausea and vomiting. *Gastroenterology* 2001;120(1):263-86. [PMID: 11208736].



## CHAPTER

# 32

## Pain—Chronic

### SYNOPSIS

*Pain* is defined by the International Association for the Study of Pain as, “an unpleasant *sensory* and *emotional* experience associated with actual or potential tissue damage, or described in terms of such damage. It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant, and therefore also an emotional experience”.<sup>1</sup> In other words pain is an inherently *subjective* phenomenon characterized by discomfort (sensory), and distress (emotional feeling).

Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage. “Many have a profound distrust of a diagnosis based on symptoms alone when the symptom is *pain*, and basic research has not uncovered a test that would yield an unequivocal sign”.<sup>2</sup> Further, it is counterproductive to speculate about whether the pain is ‘real’. It is real to the patients—if they regard their experience as pain, and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain.<sup>1, 3</sup>

Pain is generally divided into three categories: nociceptive, neuropathic, and mixed. *Nociceptive pain* develops from body tissue or organ—injured or damaged—and is further divided into somatic and visceral pain. *Somatic pain* is typically related to specific anatomic areas or structures, and therefore well-localized, aching, stabbing, or throbbing in nature, e.g. fibromyalgia, osteoarthritis, and rheumatoid arthritis. *Visceral pain* is organ based, less well localizes, dull, and cramping in nature, e.g. irritable bowel syndrome, colitis, and diverticulosis. *Neuropathic pain*, on the other hand, involves damage to the nervous system characterized as burning, tingling, and lancinating, and often occurring in the nerve dermatome, e.g. trigeminal neuralgia, postherpetic neuralgia, diabetic neuropathy, and phantom limb. This pain may be associated with sensory deficit, and occur with or without nociceptive component. Metastatic cancer pain, low back pain, non-cardiac chest pain may be of *mixed pain* origin.

Clinically, pain can be categorized as acute or chronic. In general, *acute pain* is distinguished as being of recent onset; originating from an identifiable biologic component such as an injury,

infection, metabolic, or degenerative disorder; self-limited, the pain tends to abate as the tissue heals; does not have much of psychological component; and is more amenable to pharmacologic intervention.

*Chronic pain* can be described as, “persistent or recurrent pain, lasting beyond the usual course of acute illness or injury or more than 3 to 6 months, and which adversely affects the individual’s well-being. A simpler definition for chronic pain is—pain that continues when it should not”.<sup>4</sup>

The biological component of chronic pain is less well-understood than that of acute pain. It appears that chronic pain constitutes a complex mixture of pathophysiologic factors interacting with numerous psychological, social, and cultural factors, and also influenced by past experience and cognitive function, which can modulate the patient’s pain threshold, either upward or downward (Table 32.1). The biopsychosocial factors related to chronic pain is given in Table 32.2. These characteristics necessitate a systematic multidisciplinary approach by physicians (such as neurologists, anesthesiologists, oncologists); and nonphysicians (psychologists, chiropractors, acupuncturists, and hypnotists) to achieve a satisfactory outcome. It is in this context that in the diagnosis and management of chronic pain disorders the *biopsychosocial*\* approach is very much useful.<sup>5,6</sup> However, diagnosis of the etiology for chronic pain—biological or otherwise—is crucial on several stages such as investigations, treatment, and rehabilitation. Hence, it is essential to exclude, especially progressive or serious conditions as soon as possible, so that intervention can be timely.

\* Biopsychosocial approach — symptoms are viewed as a product of multiple dynamic factors that develop synergistically in combination with certain genetic, psychological, and environmental vulnerabilities”. (Weisberg MB, Clavel AL Jr. *Why is chronic pain so difficult to treat?* *Postgrad Med* 1999; 106(6):141-64).

**Table 32.1:** Factors affecting pain threshold\*

Threshold lowered	Threshold raised
Discomfort	Relief of other symptoms
Insomnia	Sleep
Fatigue	Understanding
Anxiety	Companionship
Fear	Creative activity
Anger	Relaxation
Sadness	Reduction in anxiety
Depression	Elevation of mood
Boredom	Analgesics
Mental isolation	Anxiolytics
Social abandonment	Antidepressants

\*Source: Robert T. *Introducing Palliative Care*, 3rd ed.; Symptom Management, p.66.

**Table 32.2:** Biopsychosocial factors related to chronic pain\*\*

*Biologic factors*

- Not biologically useful
- Poorly defined, multiple pain / medical problems
- Stress response (fight or flight) not present
- Significant physical deconditioning present

*Psychosocial factors*

- Significant premorbid personality
- May be an expression of psychosis or neurosis
- Depression common
- Secondary gain present (litigation, worker’s compensation)
- Sick role present, daily activities causing pain
- Abnormal illness behavior (malingering/somatization) often present
- Physical, sexual, emotional abuse often present
- Substance abuse often present
- Significant lifestyle disturbances (marital, familial, vocational) often present
- Domestic violence often present

\*\*Adopted and modified from International Association for the Study of Pain (IASP-1994).

## DIFFERENTIAL DIAGNOSIS

### Common

#### *Musculoskeletal Disorders*

- Chronic low back pain (lumbosacral disk lesions, postlaminectomy syndromes, spondylopathies, spinal stenosis)
- Chronic neck pain (cervical spondylosis, radiculitis, stenosis, whiplash injury)
- Osteoarthritis

- Fibromyalgia
- Myofascial pain (trigger points)
- Chronic overuse syndromes (tendinitis, bursitis)
- Post-traumatic pain.

#### Neurological Disorders

- Headache (chronic daily headache, tension headache, migraine)
- Central post-stroke pain (i.e. thalamic pain, or Dejerine and Roussy syndrome)
- Polyneuropathies (alcohol, HIV)
- Nerve compression or entrapment (sciatica, carpal-tunnel syndrome).

#### Metabolic

- Diabetes mellitus
- Uremia.

#### Gastrointestinal Disorders

- Gastroesophageal reflux
- Peptic ulcer disease
- Irritable bowel syndrome.

#### Psychological Disorders

- Depression
- Anxiety
- Somatization
- Chronic fatigue syndrome
- Da Costa syndrome (neurocirculatory asthenia, effort syndrome, Soldier's heart, Gulf war syndrome)<sup>7-9</sup>

*Cancer pain syndromes* (bone pain secondary to metastasis, visceral pain secondary to mass effect).

#### Occasional

- Autoimmune (RA, polymyalgia rheumatica)
- Neurological (Postherpetic neuralgia, trigeminal neuralgia, postconcussive)
- Gastrointestinal (IBD, pancreatitis, colitis, diverticulosis)

- Metabolic (gout)
- Reproductive- extrauterine (pelvic congestion syndrome, dyspareunia, vulvodynia).

#### Rare

- Musculoskeletal (compression fracture of lumbar vertebrae, seronegative spondylosis, temporomandibular joint dysfunction, phantom limb pain)
- Neurologic (glossopharyngeal neuralgia)
- Autoimmune (temporal arteritis, polymyositis)
- Nutritional deficiencies
- Paraneoplastic disorders
- Complex regional pain syndromes (CRPS: *vide infra* ↓↓).

### INVESTIGATIONS—GENERAL

#### CBC

- Anemia due to chronic disease (normochromic microcytic).
- Leukocytosis in infective lesions.

#### ESR or CRP

- To evaluate for inflammatory conditions; elevated in temporal arteritis, rheumatoid arthritis, and malignancy.

#### Blood Glucose

- To detect and monitor diabetes mellitus.

#### Serum Calcium/Alkaline Phosphatase

- Metastatic bone disease (e.g. from breast, lung, or kidney tumor) is the commonest cause of elevated serum calcium and alkaline phosphatase levels
- In patients suspected with Paget's disease – bone-specific alkaline phosphatase is more specific.

#### Urea, Creatinine, Electrolytes

- In patients suspected with CRF, and uremic polyneuropathy.

**CPK**

- Elevated in myopathies (polymyositis, metabolic disorders, drugs, alcohol, and muscular dystrophy).

**INVESTIGATIONS—SPECIFIC<sup>†</sup>****X-ray/CT Scan**

- In patients suspected with bony abnormalities, e.g. cervical, lumbosacral disk lesions; thoracic outlet syndrome; compartment syndromes, and neoplastic lesions
- Lytic lesions may be the only finding early in Paget's disease.

**MRI**

- To further evaluate CT scan lesions related to discogenic pain; spinal canal stenosis; various bone and joint lesions; avascular necrosis, etc
- MRI is extremely helpful in the evaluation of pain that may be due to intracranial mass lesion; bony or soft-tissue lesions, abscess, metastatic deposits; facial pain due to posterior fossa lesions; facial nerve lesions; orbital pain; abdominal and pelvic pain due to inflammation or malignancy.

**Bone Scan**

- Helpful in evaluating pain due to a stress fracture, infection (osteomyelitis); and chronic pain in bone cancer patients – most commonly due to secondary deposits in spine, pelvis, extremities, ribs, and skull
- Bone scanning is the most sensitive test for evaluating the extent of lesions in the whole skeleton affected by Paget's disease.

**NCS/EMG**

- These two studies, which compliment one another, can often distinguish between neurogenic and myogenic disorders
- NCS distinguish between mononeuropathies (e.g. due to trauma, compression, or entrapment) and polyneuropathies (e.g. due to metabolic, toxic, malignant, nutritional, autoimmune, or hereditary disorders)
- In addition, they may also be helpful in excluding organic disorders when psychogenic pain or functional syndrome is suspected.

**Cancer Screen/Tumor Markers**

- Age and gender related cancer screening, e.g. breast mammography, Pap smear, PSA, etc.; and tumor markers, e.g. alpha-fetoprotein, beta chorionic gonadotropin, carcinoembryonic antigen, etc. may be helpful in the evaluation of patients suspected with cancer pain.

**CLINICAL NOTES**

- Although most patients have great difficulty in describing pain sensation, its assessment is important and helpful diagnostically. Therefore, evaluation of a patient with chronic pain should include the following:
  - Quality (pricking, lancinating, burning, etc., i.e. somatic, visceral, or neuropathic, as explained above);
  - Is it *bone pain*? Bone pain may begin as a dull, constant ache that grows worse; it feels deep with boring, stabbing, throbbing, cramping or gnawing sensation; usually increases at night and may not subside when sleeping; mostly due to metastatic deposits; referred to a different area from the site of the problem;
  - Duration (acute, chronic, constant, or intermittent);
  - Patient's functional status (i.e. the impact of pain on patient's daily activities such as

<sup>†</sup>Because of heterogeneity of the chronic pain and its presentation, specific laboratory and imaging evaluation must be targeted to specific condition and to rule out other life-threatening illnesses.

- ability to perform household chores, work tasks, leisure in interests, sleep, etc. with the help of VAS, i.e. visual analog scale;<sup>‡</sup>
- A review of previous diagnostic studies (careful reviewing of prior test reports is essential to eliminate unnecessary repetition);
  - An assessment of coexisting diseases and conditions (i.e. biological causes such as musculoskeletal, neurologic, cardiovascular, respiratory, gastrointestinal, and gynecological disease).
- The mnemonic “PQRST” is helpful when dealing with painful conditions:
    - “P” refers to precipitating or palliative factors; this information may provide clues for possible etiologies or associated disorders;
    - “Q” refers to quality of the pain (nociceptive, neuropathic, or mixed - as described above);
    - “R” stands for radiation and original location of pain; radiating pain is characteristic of neuropathic pain;
    - “S” stands for severity of pain: many specialized clinical tools in multiple languages are available for pain assessment.<sup>10</sup> Examples include unidimensional scales such as the visual analog scale (VAS), verbal rating scale (VRS), numerical rating scale (NRS), and the pain faces scale, etc. (use score 1-to-10 rating scales: severe pain is defined as pain that is rated as 7 to 10 on a 0 to 10 VAS);
    - “T” stands for timing, including onset, duration, and frequency—daily, paroxysmal, seasonal, nocturnal, or diurnal.
  - Assess patient’s psychosocial status—A good psychosocial and psychosexual history is needed when organic diseases are excluded or coexisting psychiatric disorders are suggested. Obtain sufficient history to evaluate depression; anxiety disorder; somatization; physical or sexual abuse; drug abuse/dependence; and family, marital, or sexual problems
  - History of onset—Discord in family dynamics, difficult social interactions, stressful work environment, strained marital relationship, sexual problems, and history of substance abuse, domestic violence, and absence of a clear pathophysiologic mechanism suggest a primary psychosocial cause
  - Circumstances associated with the onset of pain is important; it helps to identify whether the patient’s complaints are related to biologic process, or is predominantly psychological or psychosocial in origin
  - Physical examination—Its main purpose is to determine the possibility of underlying biologic process. Each system, particularly the ones pertaining to the patient’s presentation, and including complete mental state examination (affect, mood, ideation, and insight) is performed. Any evidence of primary biologic process responsible for chronic pain is subjected to further appropriate physical examination and investigations. Table 32.3 illustrates location-wise classification of common biological causes for chronic pain
  - Assess for Waddell’s signs<sup>11</sup> (Table 32.4), and inconsistencies in the above examination; positive Waddell’s signs generally indicate a nonphysiological etiology of pain.

<sup>‡</sup>VAS: A tool used to help a person rate the intensity of certain sensations and feelings, such as pain. The VAS for pain is a straight line with one end meaning no pain and the other end meaning the worst pain imaginable. A patient marks a point on the line that matches the amount of pain he or she feels. It can also be used to help choose the right dose of pain medicine.

## RED FLAGS

- Any patient with unexplained, persistent pain—somatic, visceral, or bone pain—should be suspected of having malignant disease and appropriate investigations performed.

**Table 32.3:** Location-wise classification of causes for chronic pain syndromes

<i>Headache/ facial pain</i>	<i>Musculo- skeletal pain</i>	<i>Low back pain</i>	<i>Abdomen/ pelvic pain</i>	<i>Peripheral nerve pain</i>
<ul style="list-style-type: none"> <li>• Migraine</li> <li>• Tension</li> <li>• Medication overuse</li> <li>• Temporal arteritis</li> <li>• Trigeminal neuralgia</li> <li>• Postconcussive</li> <li>• Chronic otitis</li> <li>• Sinusitis</li> <li>• Dentalgia</li> <li>• Meningitis</li> <li>• Abscess</li> <li>• Tumor</li> <li>• Glaucoma</li> <li>• Iritis</li> </ul>	<ul style="list-style-type: none"> <li>• Trauma</li> <li>• Osteoarthritis</li> <li>• Rheumatoid arthritis</li> <li>• Gout/pseudogout</li> <li>• Drug myositis/statins</li> <li>• Osteomyelitis</li> <li>• Bursitis/tendinitis</li> <li>• Fibromyalgia</li> <li>• Polymyalgia rheumatica</li> <li>• Polymyositis</li> <li>• Dermatomyositis</li> <li>• SLE</li> <li>• Trichinosis</li> <li>• Lyme disease</li> <li>• Paget's disease</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic disc disease</li> <li>• Osteoporotic fractures</li> <li>• Spinal stenosis</li> <li>• Seronegative spondylosis</li> <li>• Epidural abscess</li> <li>• Tumor</li> </ul>	<ul style="list-style-type: none"> <li>• IBS</li> <li>• IBD</li> <li>• Colic-biliary/renal</li> <li>• Esophagitis</li> <li>• Gastritis</li> <li>• Hepatitis</li> <li>• Pancreatitis</li> <li>• Pyelonephritis</li> <li>• Endometriosis</li> <li>• Ovarian cyst</li> <li>• Polycystic kidney</li> <li>• Mesenteric thrombosis</li> <li>• Aortic aneurysm</li> <li>• Porphyria</li> <li>• Sickle cell disease</li> </ul>	<ul style="list-style-type: none"> <li>• Diabetic neuropathy</li> <li>• Uremic neuropathy</li> <li>• HIV neuropathy</li> <li>• Toxic neuropathy</li> <li>• Paraneoplastic syndromes</li> <li>• B12 deficiency</li> <li>• Hereditary neuropathies</li> </ul>

**Table 32.4:** Waddell's signs

Waddell's signs are special nonphysiologic maneuvers used to evaluate persons when exam findings are inconsistent. They are:

1. Superficial tenderness—Skin tenderness to light palpation over a wide area
2. Nonanatomic tenderness—Deep tenderness over a wide area, crossing multiple anatomic boundaries; often extending cephalad to the thoracic spine or caudad to the sacrum
3. Axial loading—Eliciting low back pain when pressing down on the top of the patient's head.
4. Rotation—Back pain when the shoulders and pelvis are rotated passively in the same plane with the feet together. Normally, rotating the shoulders and pelvis together should not be painful as it does not stretch the structures of the back.
5. SLR—Observing an improvement of 30–40° when the patient is distracted, i.e. distracted straight leg raise, compared with formal testing.
6. Weakness—Cogwheeling, i.e. weakness that is jerky, with intermittent resistance, of many muscle groups upon manual muscle testing of strength
7. Sensory—Diminished light touch or pinprick sensation in a stocking pattern, rather than a dermatomal pattern, in an individual who is not diabetic
8. Overreaction—During the examination may be observed in several manifestations (e.g. disproportionate verbalization, facial grimacing, muscle tension and tremor, collapsing, sweating).

Although Waddell's signs can detect a nonorganic component to pain, they do not exclude an organic cause. The presence of three or more positive findings may be clinically significant in terms of psychosocial issues or possible illness behavior. Isolated positive signs are of limited value.

- Beware of the high rate of psychiatric comorbidities that exist with chronic pain disorders; and even when an organic cause for a patient's pain can be found, it is still wise to look for other factors<sup>12</sup>
- Beware of involvement of litigation or evidence of secondary gain, e.g. issues such as indemnity, loss of financial stability, and relationships
- Chronic pain may trigger fear of death, disability, or disease progression; therefore, support and education may be important even for mild pain; stress that pain does not always equal harm.

## SELECTIVE GLOSSARY

**Complex regional pain syndrome<sup>s</sup>**—The CRPS<sup>13, 14</sup> is a neurologic disorder affecting central and peripheral nervous systems—a common mechanism may be injury to central or peripheral neural tissue — such as due to head injury, stroke, tumor, burns, fractures, sprains, operative procedures, trivial soft tissue injury, vaccination, and microtrauma. Persons of all ages and both sexes are affected, and can involve

<sup>s</sup>The terms currently in favor are complex regional pain syndrome I (the equivalent of Reflex sympathetic dystrophy) and complex regional pain syndrome II, also known as causalgia.



either the arms or the legs. CRPS is characterized by pain, edema, stiffness, and discoloration. Pain is intense and burning, out of proportion to the injury, allodynia (perception of pain from a nonpainful stimulus), or hyperalgesia (disproportionate to the inciting event). Edema is usually one of the earliest findings. Stiffness may occur. Discoloration may vary from intensely erythematous to cyanotic, pale, purple, or gray. The syndrome progress through a series of stages:

*Acute stage*—Usually warm phase of 2-3 months: Pain is more severe than would be expected from the injury; burning or aching quality; may be increased by dependency of the limb, physical contact, or emotional upset. The affected area becomes edematous, may be hyperthermic or hypothermic, and shows increased nail and hair growth. Physical findings may be minimal; radiographs may show early bony changes.

*Dystrophic phase*—Vasomotor instability for several months: Edematous tissue becomes indurated; skin becomes cool and hyperhidrotic with livedo reticularis or cyanosis; hair may be lost, and nails become ridged, cracked, and brittle. Hand dryness becomes prominent, and atrophy of skin and subcutaneous tissues becomes noticeable. Pain remains the dominant feature. It usually is constant and is increased by any stimulus to the affected area. Stiffness develops at this stage. Radiographs may show diffuse osteoporosis. The 3-phase bone scan is usually positive. Duration is 3-12 months from onset.

*Atrophic phase*—Usually cold extremity with atrophic changes: Pain spreads proximally, may diminish in intensity, but persists with occasional flare-ups. Skin is thin and shiny; edema is absent; contractures may occur. Radiographs indicate marked demineralization.

The diagnosis of CRPS is excluded by the existence of any condition that would otherwise

account for the degree of pain and dysfunction. A single, reliable, sensitive, and specific diagnostic test for CRPS is not available; however, the disease is not fatal.

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## CHAPTER

# 33

## Palpitation

### SYNOPSIS

The term *palpitation* refers to conscious awareness of one's own heartbeat, usually with an increase in frequency or force, with or without irregularity in rhythm. It is generally an unpleasant feeling. However, individual patients vary greatly in sensitivity to palpitations—healthy patients may be concerned with even isolated ectopic beats, e.g. patients with cardiac neurosis; while patients with higher risks and advanced heart disease, e.g. hypertrophic cardiomyopathy may be completely unaware of serious arrhythmias such as AF and even VT. Thus, the intensity of the symptoms does not necessarily correlate with the seriousness of the underlying condition.

Palpitations mean different things to different people. It is described by a variety of sensations, e.g. pounding, thumping, fluttering, jumping, racing, or skipping a beat. It is, therefore, important to establish exactly what is meant. Though it is classically suggestive of an arrhythmia (i.e. loss or abnormality of rhythm), it occurs in a wide variety of disorders of cardiac and noncardiac origin.

Although palpitations and arrhythmias are

closely related phenomenon, they are not synonymous. The symptom of palpitation does not necessarily mean that an arrhythmia is present, e.g. sinus tachycardia with anxiety; conversely, an arrhythmia can occur without the sensation of palpitation\*—an entity described as *asymptomatic* or *silent* arrhythmia, e.g. sudden cardiac death (SCD) due to ventricular fibrillation (VF) in diabetics, and asymptomatic atrial fibrillation (AF) in untreated patients with a history of AF.

The causes of palpitation vary from benign conditions requiring no therapy to life-threatening conditions requiring urgent monitoring, treatment, and referral.

However, in the vast majority of patients, palpitation is benign, and expensive and costly investigation is not warranted. Attention to characteristics that identify patients at high risk for serious causes of palpitations will help define the much smaller percentage of patients who require more extensive diagnostic testing and management of their condition.<sup>1</sup>

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\*"All palpitations are not arrhythmias and many arrhythmias do not palpitate".

## DIFFERENTIAL DIAGNOSIS

### Common

- Physiological (sinus tachycardia with stress, exercise)
- Coronary artery disease (CAD: stable angina, unstable angina, MI, SCD)
- Left ventricular failure (LVF)
- Arrhythmias (ectopics, AF, SVT, VT, VF, WPW syndrome)
- High-output states (anemia, fever, internal hemorrhage, pregnancy)
- Psychiatric disease (generalized anxiety disorder, panic attack, depression, and somatization)
- Drugs (prescribed and abused)
- Stimulants (caffeine, alcohol, nicotine, cocaine).

### Occasional

- Metabolic disorders (hypoglycemia, hyperthyroidism, menopause, electrolyte imbalance-hypokalemia, hypomagnesemia)
- Valvular heart disease (mitral and aortic regurgitation).

### Rare

- Pheochromocytoma
- Mitral valve prolapse (MVP)
- Cardiomyopathies
- Long QT-syndrome (LQTS)
- Pacemaker syndrome (endless-loop tachycardia: *vide infra* ↓↓)
- Congenital heart disease (cyanotic heart disease, Ebstein anomaly).

## INVESTIGATIONS—GENERAL

### ECG

- Palpitations may or may not be associated with ECG changes. In the majority of patients there are no ECG changes at rest while

asymptomatic.<sup>†</sup> In the event of a patient experiencing palpitations, a concurrent ECG may be diagnostic, but this is often difficult, as the timing of palpitations may not coincide with the ECG recording.

- ECG findings between episodes can include:
  - Short PR-interval and delta waves indicating preexcitation.
  - Long QT-interval due to drugs, or long QT-syndrome.
  - Left atrial abnormality, indicating AF.
  - Marked LVF, deep septal Q waves in I, aVL, and V4-6, indicating HOCM with AF.
  - Complete heart block, LBBB, or torsade de pointes.
  - Pathological 'q' waves, indicating prior MI, and therefore a focus for ventricular arrhythmias.

### CBC

- Hb < 10 g/dl; blood smear suggestive of iron deficiency anemia.

### Blood Glucose

- Hypoglycemia (blood glucose generally < 50 mg/dl) causing palpitations

## INVESTIGATIONS—SPECIFIC

### Ambulatory ECG (AECG) Recording<sup>2</sup>/Holter Monitoring (Table 33.1)

- Generally indicated if symptoms due to arrhythmia are occurring at least daily, particularly when associated with organic heart disease. Heart rhythm is monitored for 24 to 48 hours. Patients are asked to maintain

<sup>†</sup> Although a normal ECG cannot exclude the possibility of an arrhythmia or CAD, it tends to imply preserved left ventricular systolic function.

**Table 33.1:** The indications for ambulatory ECG monitoring for symptoms of arrhythmia are as follows<sup>2</sup>:**Class I—##**

- (1) Patients with unexplained syncope, near syncope or episodic dizziness without obvious cause.
- (2) Patients with unexplained recurrent palpitation.

**Class IIb—**

- (1) Patients with episodic shortness of breath, chest pain or fatigue that is not otherwise explained.
- (2) Patients with neurologic events when transient atrial fibrillation or flutter is suspected.
- (3) Patients with symptoms such as syncope, near syncope, episodic dizziness or palpitation in whom a probable cause other than an arrhythmia has been identified but in whom symptoms persist despite treatment of this other cause.

**Class III—**

- (1) Patients with symptoms such as syncope, near syncope, episodic dizziness or palpitation in whom other causes have been identified by history, physical examination or laboratory tests.
- (2) Patients with cerebrovascular accidents, without other evidence of arrhythmia.

## Class I—general agreement is that the test is useful and effective. Class II—frequently used, but there is a divergence of opinion with respect to its utility. Class IIa—weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb—usefulness/efficacy is less well established by evidence/opinion. Class III—general agreement that the test is not useful, and in some cases may be harmful.

a diary documenting the time and describing the symptoms during the monitoring period. Subsequently the patient's symptoms are correlated with documented rhythm abnormalities.

**Electrophysiological Studies (EPS)<sup>3</sup>**

- Indicated in patients with potentially life-threatening arrhythmias and episodes of SCD with successful resuscitation; EPS assist in their subsequent management by means of antiarrhythmic drugs, pacemakers, or implantation of automatic implantable cardioverter defibrillator (AICD). Common indications/contraindications for EPS appear in Table 33.2.

**Table 33.2:** Common indications/contraindications for EPS in patients with palpitations**Investigations of symptoms**

- History of persistent palpitations of possible cardiac origin
- Recurrent, unexplained syncope of possible cardiac origin
- Presyncope with impaired left ventricular function

**Interventions**

- Potentially life-threatening arrhythmias requiring intervention
- Sustained ventricular tachycardia
- Unexplained ventricular ectopy
- Hypertrophic cardiomyopathy with ventricular tachycardia
- Uncontrolled or recurrent AF refractory to conventional therapy
- Symptomatic sinus bradycardia
- Second and third degree atrioventricular blocks
- Long QT syndrome
- Rhythm disorders in patients with pacemakers and defibrillators

**Evaluation**

- Evaluation of therapy in patients with accessory AV pathways
- Evaluation of efficacy of pharmacotherapy in patients with life-threatening arrhythmias
- Evaluation of patients for catheter ablation procedures or antitachycardia devices

**Contraindications**

- Severe aortic stenosis
- Unstable coronary disease
- Left main stem stenosis
- Substantial electrolyte disturbance

**Continuous —Loop Event Recorder**

- The event monitor is a patient activated (i.e. conventional) device. These monitors are generally worn for a period of up to 30 days, continuously recording the patient's under-lying rhythm, but require the patient to manually trigger, i.e. to activate the device to save the information. The loop recorder provides the rhythm strip generated during the two minutes preceding and following the episode of palpitation. Conventional event monitoring is successful only when the patient is aware of symptoms as they occur,

and is capable of pressing the signal button promptly. Newer event recorders have programmable automatic triggers for rapid and slow heart rates. The advantages over Holter monitoring are that, a symptom diary is not needed and the higher yield of collected data is useful for detecting arrhythmia associated with palpitation.

#### Continuous Mobile Cardiac Outpatient Telemetry (MCOT)<sup>4</sup>

- It has several advantages over traditional ambulatory monitoring systems in the diagnostic evaluation of symptoms such as palpitations, dizziness, and syncope. MCOT can detect asymptomatic clinically significant arrhythmias, and was especially useful to identify the cause of presyncope/syncope, even in patients with a previous negative workup. This outpatient monitoring system allows patients to undergo daily medication dose titration in the outpatient setting, thus avoiding hospitalization.

#### Pacemaker Evaluation

- In patients who complain of palpitation with pacemaker.

#### Exercise ECG/TMT

- Indicated in patients who are known to have or suspected to have CAD.

#### Echocardiography

- May be indicated in patients suspected of valvular heart disease, CHF, or any structural abnormality. The ACC/AHA Guidelines for the Clinical Application of Echocardiography state that, "Unless there are other indications for testing, echocardiography need not be performed in a subject with palpitation for which an arrhythmic basis has been ruled out.<sup>5"</sup> The ACC/AHA indications for echocardiography in patients with

**Table 33.3:** Recommendations for echocardiography in patients with arrhythmias and palpitations<sup>5</sup>

##### Class I

1. Arrhythmias with clinical suspicion of structural heart disease
2. Arrhythmia in a patient with a family history of a genetically transmitted cardiac lesion associated with arrhythmia, such as tuberous sclerosis, rhabdomyoma, or hypertrophic cardiomyopathy
3. Evaluation of patients as a component of the work-up before electrophysiological ablative procedures

##### Class IIa

1. Arrhythmia requiring treatment
2. TEE or intracardiac ultrasound guidance of radiofrequency ablative procedures

##### Class IIb

1. Arrhythmias commonly associated with, but without clinical evidence of heart disease
2. Evaluation of patients who have undergone radiofrequency ablation in the absence of complications (In centers with established ablation programs, a post-procedural echocardiogram may not be necessary)
3. Postoperative evaluation of patients undergoing the Maze procedure to monitor atrial function

##### Class III

1. Palpitation without corresponding arrhythmia or other cardiac signs or symptoms
2. Isolated premature ventricular contractions for which there is no clinical suspicion of heart disease

arrhythmias and palpitations are given in Table 33.3.

#### TFTs

- Hyperthyroidism is associated with AF, PSVT, and CHF.

#### Urea, Creatinine, Electrolytes

- Dehydration and hypovolemia may be associated with arrhythmias.

#### Urine

- 24 hours urine collection for vanillylmandelic acid (VMA) assay.

#### Drug Levels

- To assess for drug toxicity, e.g. digitalis.



## CLINICAL NOTES

- An important step in the evaluation of palpitation is to establish or exclude the presence of underlying structural heart disease such as CAD, CHF, valvular stenosis or regurgitation, cardiomyopathy, and congenital cardiac disorders, and to detect life-threatening cause of palpitation that place patients at risk of sudden death—VT and VF
- Any evaluation of palpitations must first confirm that the patient is hemodynamically stable, and that the symptoms are not life-threatening, which in many cases can often be made from history, physical examination, and ECG findings, which are sufficient to determine the nature of the problem
- A patient with palpitation is usually asymptomatic at the time of physical examination, and the diagnosis of arrhythmia may pose a real problem if the arrhythmia is not present at the time of examination. One solution is to request the patient to present as soon as possible at the onset of palpitation. However, if the history and physical evaluation indicates the possibility of any serious arrhythmia, it is prudent to monitor the patient (Table 33.4)
- History—In a study reported by Summerton N et al,<sup>6</sup> characteristic historical factors contributory to new-onset clinically significant palpitations include:
  - Current medical problems, e.g. thyroid disease, asthma, anemia, anxiety, depression, perimenopause
  - Past history of hypertension, CAD, valvular heart disease, congenital heart disease, cardiomyopathy
  - Family history of thyroid disease, palpitation
  - Consumptions—Cigarettes, alcohol, coffee—per day frequency, and duration
  - Current medications, e.g. benzodiazepines, ACE-inhibitors, diuretics, OHA, insulin, beta-blockers, antianginals, thyroxin, antidepressants.

**Table 33.4:** Clues to arrhythmia in clinical disorders

Clinical disorder	Clues
<ul style="list-style-type: none"> <li>• Systemic hypertension</li> <li>• Coronary artery disease</li> <li>• Heart failure</li> <li>• Diabetes mellitus</li> <li>• Bronchial asthma</li> <li>• Thyrotoxicosis</li> <li>• Congenital deafness</li> <li>• Antiarrhythmic or antidepressant drugs</li> <li>• Diuretics</li> <li>• Pre-excitation</li> </ul>	<ul style="list-style-type: none"> <li>• Vasodilators (nitrates, calcium channel blockers); pheochromocytoma</li> <li>• Ventricular arrhythmias; heart blocks</li> <li>• Digitalis toxicity; hypokalemia of diuretics</li> <li>• Hypoglycemia</li> <li>• Bronchodilators (methylxanthines, beta-agonists)</li> <li>• Sinus tachycardia, Atrial fibrillation</li> <li>• Congenital long QT syndrome</li> <li>• Acquired long QT disorder</li> <li>• Hypokalemia</li> <li>• Reentry tachycardias</li> </ul>

- Associated symptoms such as chest pain (angina, MI); dyspnea (LVF, MI, pulmonary embolism); lightheadedness, dizziness, or sweating (syncope, hypoglycemia, pheochromocytoma); may indicate hemodynamic instability and mandate further evaluation
- Evidence of anxiety or depression should be sought in patients presenting with palpitations without clinical evidence of cardiovascular disease. Psychological factors may influence the perception of palpitation as unpleasant and abnormal and thereby prompt consultation. Psychological factors should therefore be integrated into the diagnosis of palpitation
- A family history of SCD or syncope may suggest an inherited dilated or hypertrophic cardiomyopathy (HCM)<sup>†</sup>, congenital LQTS, or Brugada syndrome (BrS: *vide infra* ↓↓). In general, first-degree relatives under 40 with a family history of SCD must be investigated

<sup>†</sup> The apical variant of HCM, also known as 'Japanese or Asian variant', is rare and often poses a diagnostic challenge.



- Palpitations since childhood suggest an idiopathic SVT, WPW syndrome, or LQTS
- Resolution of symptoms due to palpitation with vagal maneuvers such as breath-holding or the Valsalva maneuver in hemodynamically stable patients suggests PSVT
- An episode of palpitation on assuming an upright position after bending over, and aborted by lying down suggest 'postural orthostatic tachycardia syndrome (POTS: *vide infra* ↓↓)', i.e. atrioventricular nodal reentry tachycardia (AVNRT)
- An episode of polyuria that follows palpitations may suggest supraventricular arrhythmias
- Palpitations associated with restlessness, warm and sweaty palms, fine tremor, protruding eyes, and enlarged thyroid (goiter) is due to hyperthyroidism
- The use of medications, drugs, and stimulants should be questioned and quantified. Almost all antiarrhythmic drugs have a proarrhythmic potential, i.e. they may worsen existing arrhythmia or provoke new arrhythmias in some patients. Phenylpropanolamine, a frequent ingredient in diet pills and cold remedies, is one of the many sympathomimetics that can cause arrhythmias. Eyedrops that include beta-blockers have been blamed in some cases of bradycardia
- Palpitations as a result of varieties of arrhythmias may be provoked by excess consumption of alcohol even in healthy individuals (holiday heart syndrome: *vide infra* ↓↓)
- Palpitations due to AF are the most common arrhythmia in the elderly (secondary to hypertension, and CAD)
- To help characterize the palpitations, requesting the patient to simulate their rhythm by tapping his finger on a hard surface can be quite informative. The physician can also help the patient by tapping out examples of rapid or irregular rhythm that has been experienced
- Physical examination—Possible evidence of organic heart disease may include: hypertension; signs of CHF (rales, cardiomegaly, acute pulmonary edema, third heart sound, jugular pressure greater than 16 cm, and positive hepatojugular reflex); and cardiac murmurs. Other signs may include tachycardia/bradycardia, pedal edema, hepatomegaly, and pleural effusion. Some clinical disorders associated with palpitations may provide clues to the nature of the arrhythmia (Table 33.5)
- Cardiac examination—Common cardiac murmurs/disorders associated with palpitation are given in Table 33.6.

**Table 33.5: Clues to the nature of palpitations**

Nature of palpitations	Clues / Clinical significance
Missed beat followed by heavy beat, or thump in the chest	Atrial or ventricular premature contraction with compensatory pause
Rapid regular palpitations (regular like a clock)	Sinus tachycardia Supraventricular tachycardia
Rapid irregular palpitations (like in an obstacle race)	Ventricular tachycardia Atrial fibrillation Atrial tachycardia with varying block
Sudden palpitations with sudden cessation (like a light switch)	Atrial flutter with varying block Paroxysmal supraventricular tachycardia Reentry tachycardia Tachy-brady of sick sinus syndrome

**Table 33.6: Cardiac murmurs and disorders associated with palpitation**

Cardiac murmurs/signs with palpitation	Disorder
Midsystolic click, often followed by systolic murmur	MVP
Triple apical impulse, loud S <sub>4</sub> , harsh, holosystolic murmur along left sternal border, increased with Valsalva maneuver, decreased with squatting, associated with mitral regurgitation, AF, VT	HOCM
Laterally displaced apical impulse, S <sub>3</sub> , S <sub>4</sub> gallop, CHF, associated with AF, VT	Dilated cardiomyopathy

## RED FLAGS

- Any person, including a child, with symptoms of palpitations, recurrent loss of consciousness, collapse associated with exertion, atypical seizures with a normal EEG, or with any documented arrhythmia must be thoroughly evaluated by cardiologists, especially to screen for inherited cardiac diseases such as WPW syndrome, HOCM, LQTS, and BrS. Screening should be considered in all first-degree relatives (parents, siblings and children) of anyone who has died under 40 yrs from an inherited heart condition or unexplained sudden cardiac episode
- Do not overlook MI, including silent MI and unstable angina as a cause of arrhythmia manifesting as palpitations, especially in the elderly
- Palpitations associated with syncope and presyncope merit a complete cardiovascular evaluation; sustained or nonsustained VT must be ruled out
- Sudden onset of palpitations in an apparently healthy person associated with ECG evidence of PSVT is suggestive of WPW syndrome. Following the termination of the tachycardia, an ECG should be performed during the sinus rhythm to screen for WPW syndrome. They need periodic observation as they are potentially at an increased risk of dangerous ventricular arrhythmias, including SCD. Although relatively uncommon, SCD may be the initial presentation in patients with tachyarrhythmias due to WPW syndrome
- Although an underlying psychiatric illness should be considered in appropriate patients, it does not obviate the need for a complete evaluation to exclude a cardiac origin of palpitation; true arrhythmias do occur in such patients; PSVT may masquerade as *panic attack*, leading to misdiagnosis<sup>7</sup>
- Sinus tachycardia recorded during palpi-

tation—in the absence of exertion or hyperdynamic states—should not be automatically attributed to anxiety; the patient could be suffering from POTS.<sup>8</sup>

## SELECTIVE GLOSSARY

**Brugada syndrome (BrS)**—Since its introduction as a clinical entity in 1992 (originally described by Pedro and Joseph Brugada), the BrS has attracted great interest because of its high incidence in many parts of the world, and its association with high risk for sudden death in young and otherwise healthy adults, and less frequently, in infants and children. Sudden and unexpected death syndrome (SUDS) of young adults during sleep is endemic in Japan and Southeast Asia. SUDS characteristics include the following: (1) victims are relatively young, healthy men leading normal lives; (2) death often occurs during sleep late at night; and (3) autopsy findings are usually negative. The syndrome typically manifests during adulthood, with a mean age of sudden death of  $41 \pm 15$  years. The youngest patient clinically diagnosed with the syndrome is 2 days old and the oldest is 84 years old. BrS is a primary electrical disease resulting in abnormal electrophysiologic activity in right ventricular epicardium. Recent genetic data linking the BrS to an ion channel gene mutation (SCN5A) provides further support for the hypothesis. The syndrome is characterized by— (a) a peculiar ST segment elevation in the right precordial leads; often accompanied by apparent conduction block in the right ventricle; (b) structurally normal heart; and (c) a propensity for life-threatening ventricular tachyarrhythmias. The higher intercostal space V (1) to V (3) lead ECG could be helpful in detecting Brugada patients. Although two types of the ST-segment elevation are present, the coved type is more relevant to the syndrome than the saddle-back type. ST segment elevation in the right chest

leads is observed in a variety of clinical settings (e.g. acute septal ischemia, pericarditis, ventricular aneurysm, and in some normal variants like early repolarization), and is not unique or highly specific for the BrS. A clear distinction cannot be made on the basis of an ECG alone. However, ST segment elevation in the right precordial leads in the absence of ischemia, electrolyte or metabolic disorders, pulmonary or inflammatory diseases or abnormalities of central or peripheral nervous system may identify the BrS. In such cases, the term “idiopathic” is appropriate. The ECG manifestations of BrS are often dynamic or concealed, and may be unmasked or modulated by sodium channel blockers (ajmaline, procainamide and flecainide), a febrile state, vagotonic agents,  $\alpha$ -adrenergic agonists,  $\beta$ -adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, hypo- and hyperkalemia, hypercalcemia, and alcohol and cocaine toxicity. Imaging techniques, endocardial biopsy and cardiac catheterization are useful in ruling out structural cardiac abnormalities. Finally, extension of the testing to family members is also important because of high incidence of familial occurrence. Currently, implantable cardiac defibrillator implantation is the only proven effective therapy in preventing sudden death in patients with the BrS, and is indicated in symptomatic patients, and should be considered in asymptomatic patients in whom VT/VF is inducible at time of electrophysiologic study.

**Holiday heart syndrome**—The association between alcohol use and rhythm disturbances, particularly supraventricular tachyarrhythmias in apparently healthy people is called “holiday heart syndrome”. The syndrome was first described in persons with heavy alcohol consumption, who typically presented at weekends or after holidays, but it may also occur

in patients who usually drink little or no alcohol. Recently, similar reports indicated that recreational use of marijuana may have similar effects. Palpitations are the most common symptom. These can be intermittent or persistent, depending on the presence or absence of sustained arrhythmia and the ventricular response to atrial fibrillation. Patients with rapid ventricular responses can present with near syncope symptoms, dyspnea on exertion, and angina. The most common rhythm disorder is atrial fibrillation, which usually converts to normal sinus rhythm within 24 hours. Atrial flutter, isolated ventricular premature beats, isolated atrial premature beats, junctional tachycardia, and various other rhythm disturbances may occur with less frequency. The holiday heart syndrome should be considered particularly as a diagnosis in patients without overt heart disease presenting with new onset atrial fibrillation. Though recurrences occur, the clinical course is benign and specific antiarrhythmic therapy is usually not warranted. Arrhythmia monitoring and observation are adequate in many patients.

**Pacemaker syndrome**—First described in 1969 by Mitsui et al as a collection of symptoms associated with right ventricular pacing. In a general sense, pacemaker syndrome can be defined as the symptoms associated with atrioventricular dyssynchrony. The symptoms of pacemaker syndrome included dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, palpitations, hypotension, pre-syncope, and even syncope. Heart failure signs include elevated neck veins, rales, and pedal edema. Physical exam can often reveal cannon A-waves. Additional symptoms attributed to pacemaker syndrome include easy fatigability, malaise, headache, and the sensation of fullness and pulsations in the head and neck. In the era of physiological dual chamber pacing, the diagnosis is often forgotten,

but pacemaker syndrome may still occur. The diagnosis of pacemaker syndrome requires a high index of suspicion and the correlation of symptoms or relative hypotension with periods of ventricular pacing. The electrocardiogram should be inspected carefully for loss of atrial capture, particularly when anti-arrhythmic drugs which increase the pacing threshold have been prescribed. In addition, environmental sources of electromagnetic interference, both within and outside the hospital environment can result in pacemaker malfunction and aggravating symptoms of pacemaker syndrome.

**Postural orthostatic tachycardia syndrome (POTS)**—It is an under recognized but persistent autonomic disorder in young patients, usually females aged 15 to 50 years, with a variety of symptoms and variable outcome. Patients with this condition exhibit orthostatic intolerance (OI) and excessive tachycardia. Excessive tachycardia with POTS has been defined as a rapid (within 10 minutes) increase in heart rate by more than 30 beats per minute or a heart rate that exceeds 120 beats per minute. Patients with POTS can experience difficulty with daily routines such as housework, shopping, eating, and attending work or school. The possibility exists that all forms of OI, including POTS, result from central hypovolemia even without tachycardia. Adults with POTS do not have hypotension, whereas children may exhibit hypotension. Many patients with POTS are intolerant of exercise. “Idiopathic” POTS must be distinguished from other conditions that can reduce venous return to the

heart and produce similar signs and symptoms such as dehydration, anemia, or hyperthyroidism.

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## CHAPTER

# 34

## Polyuria

### SYNOPSIS

*Polyuria* is a highly subjective symptom, and generally defined as the production of abnormally large amount of urine, i.e. 3 liters or more in 24 hours in an adult.\*

Under normal physiological conditions urine production is about 1-2 L per day. The chief determinant of urine volume is the intake of fluids, which in turn is influenced by individual's dietary habits, temperature, mental state, physical activity, general health, and medications.

It is important to differentiate *true polyuria* from other similar urinary symptoms such as *urinary frequency*, which is the need to urinate many times during the day or night, but in normal or less than normal volumes; and *urinary urgency*, which implies a strong desire to void urine with a sensation of impending micturition, without a concomitant increase in the volume of urine, e.g. in cystitis or benign prostatic hypertrophy. Although polyuria may also accompany *nocturia*, many individuals complaining of the latter—sometimes called as *nocturnal polyuria syndrome*—have no objective

evidence of increase in the total output of urine; this phenomenon is attributed to multiple factors, such as reversal of the normal diurnal variation in urine flow, behavioral or environmental factors, overactive bladder, and pathologic conditions, e.g. CHF, CRF, nephrotic syndrome, anxiety, primary sleep disorders, and sleep apnea.<sup>1-3</sup>

Polyuria implies water or solute (i.e. osmotic) diuresis, which can be differentiated by the estimation of urine (and also serum) osmolality.<sup>†</sup>

An average person excretes between 600 to 800 mOsm of solutes per day, primarily as urea and electrolytes. Generally, increased urine osmolality (hyperosmolality) is observed in solute diuresis (i.e. rich in solutes), and decreased values (hyposmolality) in water diuresis (i.e. poor in solutes). Table 34.1 classifies polyuria and its differential diagnosis in terms of solute verses water diuresis.

Though urine osmolality can help distinguish a solute (osmotic) from water diuresis, a urine specific gravity (Usg) by urinometer also correlates

\*Polyuria is also defined as urine output > 50 ml/kg per day.

<sup>†</sup> The urine osmolality is a measure of the concentration of the urine and is primarily determined by the level of antidiuretic hormone. Normal urine osmolality value (random sample): 100 – 1,200 mOsm/kg H<sub>2</sub>O.



**Table 34.1:** Solute vs water diuresis—differential diagnosis

<p><b>1-A—Solute (osmotic) diuresis:</b> (due to excessive filtration of a poorly reabsorbed solute)</p> <ul style="list-style-type: none"> <li>• Glucosuria (Diabetes mellitus, DKA)</li> <li>• Urea diuresis (high-protein parental infusions)</li> <li>• Mannitol or glycerol infusion</li> <li>• Radiographic contrast media</li> <li>• CRF</li> <li>• Alcohol abuse</li> </ul> <p><b>1-B—Nitriuretic syndromes:</b> (due to excessive chronic sodium loss)</p> <ul style="list-style-type: none"> <li>• Diuretics</li> <li>• Hypernatremia (IV saline)</li> <li>• Addison's disease</li> <li>• Salt-wasting nephropathy</li> </ul> <p><b>2-A—Water diuresis:</b> (too much water intake)</p> <ul style="list-style-type: none"> <li>• Psychogenic polydipsia/water intoxication/over hydration</li> <li>• Hypothalamic disease (infiltration or infarction affecting thirst center)</li> <li>• Drugs (diuretics)</li> </ul> <p><b>2-B—Inability of kidneys to conserve water CDI (vasopressin sensitive):</b></p> <ul style="list-style-type: none"> <li>• Pituitary ablation, tumor, cyst, aneurysm, trauma, meningitis, hemorrhage, thrombosis, metastasis, Sheehan's syndrome.</li> </ul> <p><b>2-C—NDI (vasopressin insensitive):</b></p> <ul style="list-style-type: none"> <li>• Acquired tubulointerstitial renal disease (e.g. hypercalcemia, hypokalemia, analgesic nephropathy, obstructive uropathy)</li> <li>• Drugs (lithium)</li> <li>• Genetic disorders</li> </ul>
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with urine osmolality and gives important information that reflects the concentrating ability of the kidneys, provided there is no reason to suspect increased excretion of larger solutes such as glucose, urea, radiocontrast media, etc. A random early morning Usg of 1020 (700 mOsm/kg) or more in the absence of sugar or protein excludes a serious concentrating defect. However, urine osmolality is a better measurement of renal hydration status than Usg.<sup>4,6</sup>

When the initial evaluation fails to establish the cause of polyuria, a water deprivation test is necessary. Further, a vasopressin test enables the differentiation between cranial diabetes insipidus, i.e. CDI, and nephrogenic diabetes insipidus, i.e. NDI. (Table 34.2).

**Table 34.2:** Differential diagnosis of diabetes insipidus

<i>Cranial diabetes insipidus</i>	<i>Nephrogenic diabetes insipidus</i>
<p><b>Trauma</b> (head injury)</p> <p><b>Vascular</b></p> <ul style="list-style-type: none"> <li>• Hemorrhage/thrombosis</li> <li>• Aneurysm</li> <li>• Sheehan's syndrome</li> </ul> <p><b>Infections</b></p> <ul style="list-style-type: none"> <li>• Meningitis</li> <li>• Encephalitis</li> <li>• Cerebral abscess</li> </ul> <p><b>Granulomatous disease</b></p> <ul style="list-style-type: none"> <li>• Tuberculosis</li> </ul> <p><b>Sarcoidosis</b></p> <ul style="list-style-type: none"> <li>• Langerhans cell histiocytosis</li> </ul> <p><b>Tumors</b></p> <ul style="list-style-type: none"> <li>• Craniopharyngioma</li> <li>• Metastases (from breast)</li> </ul> <p><b>Postsurgical</b></p> <ul style="list-style-type: none"> <li>• Removal of pituitary adenoma</li> </ul> <p><b>Postradiotherapy (cranial)</b></p> <p><b>Familial</b></p> <ul style="list-style-type: none"> <li>• DIDMOAD</li> </ul> <p><b>Idiopathic</b></p>	<p><b>Drugs</b> (lithium, demeclocycline)</p> <p><b>Renal disease</b></p> <ul style="list-style-type: none"> <li>• Renal tubular acidosis</li> <li>• Pyelonephritis</li> <li>• Polycystic kidney disease</li> </ul> <p><b>Metabolic</b></p> <ul style="list-style-type: none"> <li>• Hypercalcemia</li> <li>• Hypokalemia</li> </ul> <p><b>Postrenal transplantation</b></p> <p><b>Sickle cell disease</b></p> <p><b>Genetic defect</b></p> <ul style="list-style-type: none"> <li>• Sex-linked recessive</li> </ul> <p><b>Psychogenic polydipsia</b></p> <ul style="list-style-type: none"> <li>• Compulsive water drinking</li> <li>• Schizophrenia</li> </ul> <p><b>CNS disease</b></p> <ul style="list-style-type: none"> <li>• Multiple sclerosis</li> </ul> <p><b>Idiopathic</b></p>

## DIFFERENTIAL DIAGNOSIS

### Common

- Diabetes mellitus (undiagnosed, poorly controlled, Type 1, diabetic ketoacidosis)
- Diuretic therapy (loop diuretics, mannitol)
- Hyperalimentation therapy (amino acids, glucose)
- Chronic renal failure
- Analgesic nephropathy
- Hypercalcemia (osteoporosis treatment, bony metastasis, hyperparathyroidism)
- Alcohol abuse (beer potomania<sup>†</sup>)
- Anxiety (acute).

### Occasional

- Recovering obstructive uropathy
- Recovering acute tubular necrosis (acute renal failure)
- Drugs (lithium, antibiotics: Demeclocycline; antifungals: Amphotericin; antineoplastic; and antivirals agents)

<sup>†</sup>The ingestion of large quantities of beer, sometimes referred to as *beer potomania* or binge beer drinking, can produce polyuria with associated hyponatremia that may be severe enough to produce CNS symptoms ranging from confusion to seizures and stupor.



- CNS disorders (infections: meningitis, cerebral malaria,<sup>7</sup> HIV; mass lesions; trauma; postneurosurgery status).

**Rare**

- Psychogenic polydipsia (obsessive compulsive disorder, schizophrenia)
- Drug-induced thirst (anticholinergics, leading to excessive water drinking)
- AV nodal re-entry tachycardia
- Radiographic contrast media
- Multiple endocrine neoplasia
- Sick cell anemia
- Genetic defects (Wolfram syndrome, i.e. WS or DIDMOAD syndrome: *vide infra* ↓↓).

**INVESTIGATIONS—GENERAL****Urinalysis**

- Glucose and possible ketones in diabetes mellitus
- Leukocytes, proteinuria, hematuria with renal disorders
- Usg-Very low in diabetes insipidus (DI) and psychogenic polydipsia.

**CBC**

- Normochromic anemia in CRF
- Peripheral smear may show sickle cells.

**Blood Glucose**

- Fasting, 2 hours post 75 g oral glucose, and HbA1c. To confirm and monitor diabetes mellitus.

**24-hour Urine Specimen**

- The total volume must exceed 3L in 24 hours and helps to avoid errors attributable to variations in circadian rhythm and also to differentiate from urinary frequency
- The usual method followed (in adults) is as below:
  - On day 1, urinate into the toilet on getting up in the morning,

- Afterwards, collect all urine in a special container for the next 24 hours,
- On day 2, urinate into the container on getting up in the morning,
- Cap the container. Keep in the refrigerator or in a cool place during the collection period.

**Serum Urea, Creatinine, Electrolytes**

- Plasma urea, creatinine levels increased in renal failure
- High level of serum sodium suggests CDI and NDI
- Low levels of sodium suggest NDI or compulsive water drinking.

**Serum Calcium**

- Hypercalcemia causes solute (osmotic) diuresis and NDI.

**Ultrasound**

- To assess renal size, obstruction, tumors, and cysts
- Contracted kidneys with loss of corticomedullary differentiation in CRF.

**INVESTIGATIONS—SPECIFIC****24-hour Urinalysis**

- Estimation of various urine components permit calculation of the solute excretion rate and thus lead to the cause of polyuria. These tests may include: Volume, specific gravity, osmolality, urea, creatinine, electrolytes, calcium, glucose, ketones, and drug screen for example, mannitol, and glycerol.

**Water Deprivation Test<sup>§</sup>**

This test is indicated to differentiate between CDI and NDI – their both partial versus complete

<sup>§</sup>Contraindicated in volume depleted patients and in the presence of hypernatremia.

versions—in a well-hydrated patient, who is likely to have one or the other. Steps include:

1. After an overnight solid food and water (liquids) restriction<sup>\*\*</sup>, frequent (hourly) body weight, and urine osmolarity are measured, until 2-3 successive stable values of urine osmolarity are obtained or weight loss exceeds 3-5%. At this point the test is completed (or terminated). These values represent the patient's maximum baseline osmolarity, and under these conditions urine osmolarity should be > 800 mOsm/kg. A value < 200 suggest severe NDI or CDI; a value between 200-800 may reflect partial NDI or CDI.
2. Desmopressin acetate, i.e. DDAVP (1-deamino-8D-arginine vasopressin), is given in an initial dose of 5-10 mcg. intranasally (or 1 mcg subcutaneously or intravenously). Two more hourly urine osmolarities are recorded to determine response to exogenous hormone:
  - Urine osmolarity markedly increased → CDI.
  - Urine osmolarity — slight or no response → NDI.
- However, measuring osmolarity of plasma/urine after water deprivation test does not distinguish partial NDI from psychogenic polydipsia.

#### Plasma Vasopressin (ADH)

- When results are ambiguous, the plasma vasopressin assay is a useful adjunct in the diagnosis of DI and psychogenic polyuria:
  - Low levels are consistent with CDI (partial or complete).

- High levels in NDI (partial or complete); primary psychogenic polydipsia; ectopic ADH syndrome; certain drugs, e.g. chlorpropamide, phenothiazine.
- The expected response is given in Table 34.3.<sup>8</sup>

#### US of Neck

- May be useful to locate parathyroid adenoma in patients with hyperparathyroidism.

#### CT/ MRI

- Of brain—for evidence of pituitary-hypothalamic tumors
- Of parathyroid—for evidence of adenoma.

#### Renal Biopsy

- May be indicated in patients with unexplained polyuria, e.g. autoimmune disorders, acute tubular necrosis, and to diagnose renal dysfunction in transplanted kidney.

#### CLINICAL NOTES

- The first differentiation that needs to be clarified is that: 'Is it truly polyuria or just urinary frequency?
- History can sometimes distinguish true polyuria (i.e. frequent passage of large quantity of urine) from frequency of urination (i.e. frequent passage of small amounts of urine). If essential, a 24 hours urine collection (see above) objectively confirms true polyuria when volume is > 3 L. Associated symptoms include polydipsia, urgency, frequency, nocturia, and incontinence
- Massive polyuria (10-20 L/day) is usually due to DI, diabetes mellitus, (especially Type 1), or psychogenic polydipsia
- Mild polyuria would suggest mild diabetes mellitus, chronic nephritis, renal tubular acidosis, and hyperthyroidism
- A transient polyuria is sometimes noticed in migraine, asthma, and supraventricular tachycardia

<sup>\*\*</sup>In patients producing > 10 L of urine/day, water restriction is only done during the day under close supervision and is not done after midnight.

**Table 34.3:** Classification of causes of diabetes insipidus on basis of water deprivation <sup>8</sup>

<i>Clinical state</i>	<i>Water deprivation</i>		<i>Endogenous ADH Plasma level*</i>	<i>Exogenous ADH effect on Urine Osm.</i>
	<i>Plasma Osm*</i>	<i>Urine Osm*</i>		
Normal	>3% rise	>800	High	None
Cranial DI				
Complete	>3% rise	<200	Absent	Increase >30%
Partial	>3% rise	300–700	Low	Increase >10%
Nephrogenic DI				
Congenital	>3% rise	<300	High	None
Acquired	>3% rise	300–700	High	None
Primary/psychogenic	>3% rise	>600	High	Increase <10%
Polydipsia				

POsm = Plasma osmolality (mOsm/kg); UOsm = Urine osmolality (mOsm/kg); \* = At the end of water deprivation period, prior to exogenous vasopressin, administration.

- Abrupt onset of polyuria with craving for ice water (due to stimulation of osmoreceptors in the back of the throat) suggests CDI, e.g. due to pituitary disorders. Nocturia is common
- The next step, i.e. after confirming true polyuria is: Is this water diuresis or solute diuresis? Generally:
  - Urine osmolality > 350 mOsm/L suggests solute diuresis,
  - Urine osmolality < 250 mOsm/L suggests water diuresis, and
  - Urine osmolality between 250–350 mOsm/L may be due to either water or solute diuresis. This differentiation can be by calculating total solute excretion on a 24 hr urine collection (see 24 hr urinalysis above).
- Further, water diuresis needs to be differentiated from CDI and NDI. Patient's history, investigations, and in selected cases water restriction test/ desmopressin test help to achieve this objective
- History of head trauma; transsphenoidal surgery; CNS disease (e.g. meningitis, tuberculosis, CVA, multiple sclerosis, parkinsonism, pituitary-hypothalamic tumor, metastatic deposits); psychiatric illness, diabetes mellitus, renal disease (e.g. chronic nephritis); malignancy (hypercalcemia); endocrine and autoimmune disease is an important lead to the diagnosis of CDI / NDI
- Drug history — A significant number of drugs precipitate polyuria by various mechanisms. Over-vigorous diuretic therapy in edematous states is a common cause of polyuria. Anticholinergics produce dryness of mouth; patients may therefore ingest excessive quantity of water, causing polyuria. Nephrotoxic drugs such as NSAIDs, ACE inhibitors, aminoglycosides may precipitate acute tubular necrosis, which can result in severe polyuria in the recovery phase. Opiates inhibit ADH secretion and may produce CDI, whereas lithium and demeclocycline may produce NDI
- Physical examination should include evaluation of the following:
  - Hydration status, i.e. body weight, pulse, BP, mucous membrane, skin turgor, and urine output.
  - Signs of malignancy, e.g. cachexia, lymphadenopathy, palpable mass.
  - Target organ involvement, e.g. retinopathy, neuropathy with diabetes mellitus.
  - Abdomen — for mass and organomegaly.
  - Neurologic exam — to evaluate neurologic deficit associated with mass lesion, encephalopathy.

- Genitourinary exam — for penile, scrotal, testicular, prostate, and pelvic masses.
- NDI—The characteristic features are:
  - An inability to concentrate urine adequately with fluid restriction,
  - The occurrence of dilute urine in the presence of normal or increased osmolality, and
  - Lack of responsiveness to vasopressin.
- CDI—The characteristic features are:
  - Dilute urine,
  - Mild hyperosmolality, and
  - Responsiveness to vasopressin.
- Psychogenic polydipsia—Typically:
  - Both the serum and urine osmolality are low, and
  - Lack of responsiveness to vasopressin.

### RED FLAGS

- Think beyond diabetes mellitus in patients with polyuria with urine negative for glucose, consider DI. Review history; refer for more detailed investigations as indicated
- Unexplained polyuria in any patients with hypercalcemia—investigate for multiple endocrine neoplasia (Chapter 14, Page no. 95 “Dyspepsia”). Review family histories in detail endocrine tumors (thyroid, parathyroid, pituitary) are often present in other family members
- Beware of complications in patients with psychogenic polydipsia. Though DI has not been reported to result in renal failure, psychogenic polydipsia may result in water intoxication, leading to hyponatremic encephalopathy with headache, weakness, nausea, vomiting, diarrhoea, confusion, seizures, coma, and even death.

### SELECTIVE GLOSSARY

**Wolfram syndrome (WS)**— It is a rare, autosomal recessive, and neurodegenerative disease. The

syndrome is also known as DIDMOAD, the acronym for diabetes insipidus, diabetes mellitus, optic atrophy and deafness, which summarizes the main clinical features in WS patients, although some patients have additional clinical findings including ataxia, hypogonadism, hydronephrosis and psychiatric illnesses. The gene associated with the syndrome, called WFS1, is located in the 4p16.1 region. Patients present with diabetes mellitus followed by optic atrophy in the first decade, cranial diabetes insipidus and sensori-neural deafness in the second decade, dilated renal outflow tracts early in the third decade, and multiple neurological abnormalities early in the fourth decade. Other abnormalities include primary gonadal atrophy. Death occurs prenatally, often from respiratory failure associated with brainstem atrophy. Most patients eventually develop all complications of this progressive, neurodegenerative disorder. Though there is no treatment to reverse the underlying mechanism of neurodegeneration, early diagnosis and adequate hormonal replacement could improve quality of life and survival.<sup>9, 10</sup>

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## CHAPTER

# 35

## Pruritus

### SYNOPSIS

*Pruritus*\* is defined as an unpleasant cutaneous sensation that provokes the desire to scratch or rub the skin to obtain relief. As a physiological nociception, pruritus leads to the removal of harmful agents such as insects, and irritant substances such as dust and dirt from the skin surface, and thus helps defend the skin against harmful external agents.

Pruritus is the cardinal symptom of most dermatologic disorders, and may be further qualified as burning, tingling, or pricking by the patient. In addition to the skin, it can occur on any epithelial surface, such as the conjunctiva (e.g. allergic conjunctivitis); oropharynx (due to food allergy, or *oral allergic syndrome*:<sup>1</sup> *vide infra* ↓↓); and anogenital region (see below). It may be localized, generalized, paroxysmal, or unremitting. It may be associated with a primary dermatological disorder, or manifest as a symptom of an internal systemic process.

Based on advances in the understanding of the peripheral and central origin, itch is classified

into four categories: cutaneous itch (*pruritoceptive*, e.g. scabies, urticaria, insect bite, dermatitis); neuropathic itch (e.g. postherpetic neuropathy, multiple sclerosis); neurogenic itch (e.g. cholestasis, uremia); or psychogenic (e.g. delusional state of parasitophobia).<sup>2</sup>

Most pruritic disorders can be diagnosed with high degree of accuracy based on history, physical features of dermatosis, and appropriate investigation. However, a minority of patients presenting with itching *per se*, without any rash, or with scanty clinical findings can pose a particularly challenging diagnostic and therapeutic dilemma, besides significantly affecting their quality of life.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Urticaria
- Psoriasis
- Atopic dermatitis<sup>†</sup> or atopic eczema

\*Some authors use the term *itch* if there are skin lesions expressed, and *pruritus* if there are no primary skin alterations, known as "*pruritus sine materia*"; however, its common practice to use these two terms—pruritus and itch—as synonyms.

<sup>†</sup>The terms *atopic dermatitis* and *atopic eczema* have been used synonymously; however, *dermatitis* denotes inflammation of the skin, and *eczema*, besides itching, shows ill-defined areas of redness, scaling, crusting, and lichenification. *Dermatosis* is defined as any disease of the skin in which inflammation is not necessarily a feature.



- Irritant contact dermatitis (e.g. soaps, chemicals, cosmetics, jewelery, latex)
- Food allergy (peanuts; eggs; food additives, preservatives, and flavoring agents)
- Drug allergy/hypersensitivity (aspirin, opiates)
- Miliaria (prickly heat)/sunburn/solar dermatitis
- Infections (folliculitis; dermatophytosis, e.g. tinea corporis, tinea cruris, tinea pedis)
- Infestations and bites (scabies, pediculosis, ticks, honeybees)
- Intestinal parasites/helminthic infections (hookworm, giardia, strongyloidiasis, trichinosis, cutaneous larva migrans)
- Lichen planus
- Lichen simplex chronicus
- Dry skin (asteotc dermatitis)
- Aging (senile pruritus).
- Primary biliary cirrhosis
- Hypereosinophilic syndrome
- Cutaneous T cell lymphoma (Mycosis fungoides)
- Systemic carcinoma
- Psychogenic (anxiety, depression, psychosis, delusion of parasitosis: *vide infra* ↓↓, dermatitis artefacta).

## INVESTIGATIONS—GENERAL

### CBC

- Microcytic hypochromic anemia with IDA
- In PVR: RBC count increased (often 7 to 10 million/cu mm), hematocrit above normal (at times >60%), increased Hb, WBC and platelet counts also invariably elevated
- Eosinophilia with atopy, or intestinal helminthic infection.

### Urinalysis

- May reveal proteinuria, hematuria, and granular or red blood casts in patients with renal disease.

### Stool Examination

- Ova and/or cysts of helminthic or protozoan disease may be found
- Stool for occult blood in patients aged 40 years or older. A positive result suggests possible malignancy in the GI tract.

### Microscopy of Skin Scrapings

- The mite, ova, and feces may be identified under light microscope in Scabies infestation.

### Potassium Hydroxide (KOH) 10-20% Mounts

- For evidence of hyphae, and spores of dermatophytes.

### Occasional

- Uremic pruritus
- Cholestatic pruritus (extrahepatic obstruction, hepatic failure, cirrhosis)
- Infections (HBsAg, HCV, HIV)
- Pregnancy (i.e. pruritus gravidarum, or cholestasis of pregnancy)
- Postmenopausal.

### Rare

- Ichthyosis
- Dermatitis herpetiformis
- Endocrine disorders (hyperthyroidism, hypothyroidism, carcinoid syndrome, diabetes mellitus, hyperparathyroidism)
- Hematological disorders (IDA, pernicious anemia, leukemia)
- Neurologic disorders (poststroke pruritus<sup>3</sup>)
- Myeloproliferative disorders (polycythemia rubra vera, i.e. PVR; multiple myeloma)
- Lymphomas (Hodgkin's and non-Hodgkin)
- Mastocytosis

**Blood Glucose**

- Elevated with diabetes mellitus.

**Serum Calcium**

- Elevated with hyperparathyroidism secondary to renal disease, paraneoplastic syndromes, malignancies, and Paget disease.

**LFTs**

- Elevated conjugated serum bilirubin, alkaline phosphatase, AST, ALT, and PT with hepatic cholestasis, cirrhosis, and viral hepatitis.

**Blood Urea, Creatinine, Electrolytes**

- Elevated urea, creatinine, and hyperkalemia with chronic renal failure.

**TFTs**

- Low TSH and high T4 with hyperthyroidism; high TSH with low T4 with hypothyroidism.

**CXR**

- May reveal hilar lymphadenopathy, or a mass lesion in patients with Hodgkin's disease, or bronchogenic carcinoma.

**INVESTIGATIONS—SPECIFIC****Serum Ferritin**

- Decreased values confirm IDA; low serum ferritin levels in elderly patients with chronic pruritus may assist in diagnosing malignancy.

**Serology**

- To rule out HBV (HBsAg), HCV (anti-HCV), and HIV infection in patients with risk factors.

**Serum Protein Electrophoresis**

- To screen for myeloproliferative disorders, and paraproteinemias.

**Urine for 5-Hydroxyindoleacetic Acid (5-HIAA)**

- Increased levels of urinary 5-HIAA may be detected in patients with liver metastasis, or carcinoid syndrome.

**Antimitochondrial Antibody**

- Positive for most patients with primary biliary cirrhosis.

**US Abdomen**

- Dilated bile ducts indicate biliary obstruction; the site and cause of obstruction may be visualized. Decreased renal size in chronic renal disease and in patients suspected with polycystic kidney disease, multiple cysts may be visualized. US of the neck provides information regarding enlarged parathyroid glands, thyroid nodules, and lymph nodes.

**HRCT—Chest and Abdomen**

- HRCT of the chest (when abnormal findings are noted on CXR examination) to confirm hilar lymphadenopathy or mass lesion in patients with Hodgkin's disease, or bronchogenic carcinoma respectively. HRCT of the abdomen and pelvis to visualize the mesenteric, hepatic, portal, and splenic hilar lymph nodes in patients with Hodgkin's disease and non-Hodgkin's lymphoma.

**ERCP (Endoscopic Retrograde Cholangiopancreatography)**

- Should be performed in patients suspected with primary sclerosing cholangitis, choledocholithiasis, or obstructive malignancy.

### Lymph Node Biopsy

- Presence of *Reed-Sternberg cells* is characteristic of Hodgkin's disease.

### Bone Marrow Aspirate and Biopsy

- May be indicated to establish the presence of myelofibrosis (e.g. PVR, chronic myeloid leukemia).

### Skin Biopsy for Direct Immunofluorescence with Special Stains

- May be needed to confirm primary dermatologic conditions such as dermatitis herpetiformis, mycosis fungoides, Paget's disease of the nipple, and bullous pemphigoid; or to confirm a systemic cause such as mast-ocytosis.

### Radioallergosorbent Tests (RASTs) or Patch Test

- Positive patch test may support offending cause for allergic contact dermatitis.

### Tumor Markers

- Age appropriate cancer screening such as PSA, alfa fetoprotein may be indicated in few patients with obscure cause.

## CLINICAL NOTES

- History suggests whether pruritus is primary (i.e. dermatological), or secondary (i.e. systemic), and often provides clues to its cause. Common questions include the following:<sup>‡</sup>
  - Location, duration, and timing of symptoms of pruritus, e.g. day, night, seasonal, at work, or at home.
  - Provocative factors, e.g. itching onset or

worsening in winter suggest xerosis; itching worse in the evening may be associated with scabies; itching awakening the patient at night may represent systemic disease; *bath itch*, i.e. itching that typically occurs during cooling after a hot shower may precede the development of PVR by several years.

- Drugs (erythromycin, INH, anabolic steroids, oral contraceptives), including recreational drugs (opioids, alcohol)—current and/or recent past.
  - Ingestion of any unusual or new foods.
  - OTC products the patient uses on his/her skin, or scalp.
  - Menstrual history—in women of child-bearing age.
  - History of any systemic illness (bronchial asthma; thyroid, hepatic, or renal disorder; erythropoietic porphyria, HIV).
  - History of any psychiatric illness, emotional stress.
  - History of recent travel (hepatitis, helminthic, or parasitic infection).
  - History of previous skin disease (e.g. vitiligo, ichthyosis) or atopy.
  - The work environment (chemicals, irritants).
  - Home environment—other members experiencing itching, pets, carpet in bedroom.
- The diagnosis of most pruritic disorders is possible on the basis of pattern distribution, i.e. basic morphology, shape, size, color, and predilection to specific sites of the skin. Tables 35.1 and 35.2 illustrate common causes of localized and generalizes pruritus
  - In addition to the skin, examination of other organ systems for organomegaly, lymphadenopathy, goiter, pregnancy, and signs of anemia, arthritis, or psychiatric disorders is important
  - Pruritus associated with generalized rash is common with urticaria, atopic dermatitis,

<sup>‡</sup>A structured questionnaire such as 'Eppendorf itch questionnaire' is found to be a valuable tool for evaluating chronic idiopathic pruritus and its unique features (Ref. PMID: 12100181).

**Table 35.1:** Differential diagnosis of localized pruritus

- Scalp/neck
  - Seborrheic dermatitis
  - Lichen simplex
  - Psoriasis
- Trunk
  - Urticaria
  - Contact dermatitis (axillae, waistline)
  - Erythrasma
  - Psoriasis (periumbilical)
  - Scabies
  - Seborrheic dermatitis
- Inguinal region
  - Candida
  - Contact dermatitis
  - Erythrasma
  - Pediculosis
  - Scabies
  - Tinea cruris
- Genital (i.e. scrotal, anal, or vulval) region
  - Local irritants (fabrics, tampons, sanitary wear)
  - Intertrigo (excessive perspiration, moisture)
  - Contact dermatitis (hygiene products, barrier contraceptives, douches)
  - Lichen simplex
  - Candidiasis
  - Dermatophytes (Tinea cruris)
  - Parasites (pinworm, scabies, pediculosis, trichomoniasis)
  - Venereal (herpes, gonorrhea, chancroid, LGV, syphilis)
  - Bacterial (erythrasma)
  - Anorectal disease (hemorrhoids, fissure, fistula, rectal prolapse, polyps, warts, malignancy)
  - Dermatologic disease (Psoriasis, seborrheic dermatitis, atopic dermatitis)
  - Valval disease (atrophic vulvovaginitis; VIN, i.e. vulva intraepithelial neoplasia; malignancy)
- Hands
  - Contact dermatitis
  - Scabies
  - Eczema
  - Dermatitis herpetiformis (elbows)
- Legs
  - Stasis dermatitis (venous eczema)
  - Atopic dermatitis (popliteal fossa)
  - Dermatitis herpetiformis (knees, buttocks)
  - Lichen simplex chronicus (malleoli)
  - Neurotic excoriation
- Feet
  - Intertrigo
  - Contact dermatitis
  - Pitted keratolysis
  - Tinea pedis

**Table 35.2:** Differential diagnosis of generalized pruritus

- Dermatologic disease
  - Urticaria
  - Xerosis (dry skin)
  - Atopic dermatitis
  - Contact dermatitis
  - Bullous pemphigoides
  - Dermatitis herpetiformis
  - Mastocytosis
- Drugs/food hypersensitivity
  - Aspirin, NSAIDs
  - Antibiotics, chemotherapeutics
  - Nitrates, monosodium glutamate (food preservatives, flavoring agents)
- Infective disease
  - Scabies
  - Pediculosis
  - HIV/AIDS
- Parasitic infections
  - Hookworm, pinworm, ascariasis
  - Giardiasis
  - Oncocerciasis
- Systemic disease
  - Chronic renal failure (uremic pruritus)
  - Intrahepatic cholestatic pruritus (e.g. viral hepatitis, drug-induced cholestasis, carcinoma of liver, biliary cirrhosis)
  - Extrahepatic cholestatic pruritus (e.g. common bile-duct calculus, stricture, carcinoma of pancreas)
  - Pruritus gravidarum
- Endocrine disorders
  - Hyper- and hypothyroidism
  - Hyperparathyroidism
  - Diabetes mellitus
  - Gout
- Hematopoietic disorders
  - IDA
  - PVR
- Malignancy
  - Hodgkin's lymphoma
  - Non-Hodgkin's lymphoma
  - Leukemia
  - Carcinoid syndrome
- Psychiatric disease
  - Delusion of parasitosis
  - Depression

scabies, and pemphigus. Presence of hepatomegaly or jaundice is indicative of obstructive jaundice, hepatitis, malignancy of liver, or biliary cirrhosis. Symptoms of polyuria, polyphagia, and polydipsia would suggest

diabetes mellitus, hyperthyroidism, and pregnancy. Fine stippling (pitting) of the nails is highly suggestive of psoriasis

- Signs—Common dermatological signs in pruritic disorders are described in Table 35.3
- Of all the malignancies known to induce pruritus, Hodgkin's disease is the most common
- Carcinoma of any organ may produce itching, but this is most frequently associated with involvement of the stomach, liver, and pancreas
- Pruritus of the nostrils is characteristic of fourth-ventricle tumors of the brain; it can be extremely severe and is a sign of an advanced tumor
- Hyperthyroidism is the most common cause of endocrine pruritus
- Patients with Parkinson's disease, patients who become acutely ill and are hospitalized, and patients with HIV infection often have seborrheic dermatitis
- Uremic pruritus is most often seen in patients receiving hemodialysis. However, the condition is not due to elevated serum urea levels. Pruritus is relatively absent in persons with acute renal failure
- Dermatitis herpetiformis is usually associated with celiac disease (i.e. gluten sensitive enteropathy, which commonly presents with gastrointestinal symptoms including chronic diarrhea, weight loss, abdominal bloating and anorexia, and deficiency related signs to malabsorption of iron, folic acid, vitamin B<sub>12</sub> and vitamin D, such as osteoporosis)
- While dealing with dermatological diseases suspected due to psychiatric disorder, physicians should be aware that the skin lesions are often an appeal for help; direct confrontation should be avoided if possible, and instead, a supportive environment and a stable physician-patient relationship should

**Table 35.3:** Physical signs in pruritus

<i>Sign</i>	<i>Comments</i>
Auspitz sign	Removal of scales causing punctate bleeding spots, e.g. psoriasis, actinic keratosis.
Butterfly sign	A sign on the back of the patient, i.e. upper mid-back area between the scapula, of relative hypopigmentation or normal skin in combination with areas of postinflammatory hyperpigmentation in surrounding locations accessible to the patient's hands. As most patients cannot reach the upper mid-back area between the scapulas, an examination of this area can help ascertain if a skin disease is present, because any lesions found in that area are unlikely to have been caused by scratching. Conversely, if the skin there is clear but the surrounding area is damaged, this is a strong indicator of an organic or psychological disorder.
Darier's sign	Yellowish brown or brown black macules or plaques which tend to become red, itchy, and urticate easily if they are rubbed, e.g. urticaria pigmentosa (cutaneous mastocytosis).
Dermographism (skin writing)	Light pressure or rubbing causing widespread weal-and-flare reactions with itching and burning; e.g. atopy, thyroid diseases, diabetes, menopause, infectious, systemic or malignant diseases, scabies, drug reaction, and psychic disorders.
Köbner phenomenon	Development of new plaques in response to external trauma, e.g. psoriasis, lichen planus, bullous pemphigoides, sarcoidosis, Kaposi's sarcoma.
Leser-Trélat sign	An abrupt appearance of multiple seborrheic keratoses (also known as seborrheic warts, keratosis pigmentosa, and verruca senilis) that rapidly increase in their size and number. Pruritus may be the only symptom of the sign of Leser-Trélat. This sign is linked to a variety of cancers but is it's rare, even among patients with cancer.
Nikolsky's sign	Pressure applied in a sliding motion to the lateral aspect of the blister leads to extension of the blister and or removal of the epidermis in the area

*Contd...*

Contd...

	immediately surrounding the blister. In pemphigus vulgaris this sign is positive, whereas in bullous pemphigoides it is absent.
Wickham's striae	Intensely pruritic, violaceous, flat, polygonal, well-demarcated papules of variable size, marked by criss-cross whitish streaks, e.g. lichen planus.

be fostered, often initially through short frequent office visits.<sup>4, 5</sup> Once the patient establishes trust in the physician by means of a stable relationship, the physician can help recognise the psychological impact of the disorder and recommend consultation with a psychiatrist.

### RED FLAGS

- Itching in elderly individuals, especially persistent and generalized itching, should be screened for an underlying systemic disease (see table above), including malignancy.
- The incidence of non-Hodgkin's lymphoma is significantly increased in patients with dermatitis herpetiformis.<sup>6</sup>
- If lesions of atopic eczema involve the nipple, which may be either retracted or obliterated, Paget's disease must be excluded by biopsy. Unilateral eczema may be the only indication of a ductal adenocarcinoma.
- Psychopathologic dermatological disorders such as delusion of parasitosis, psychosis; as well as due to systemic disease such as HIV, uremic pruritus, carcinoid syndrome can be severe enough to cause the patient to commit suicide.<sup>7</sup>

### SELECTIVE GLOSSARY

**Oral Allergy Syndrome (OAS)**<sup>8</sup>—History of OAS goes back to 1987 year, when Amlot for the first time used this name for pollen-food cross-reactive reactions. Since then many kinds of

reactions between pollens and different food have been described. The OAS is an adverse reaction to the ingestion of certain “trigger” foods (fresh, raw fruits or vegetables), and is especially prevalent in atopic individuals such as in people with asthma or hay fever. Most patients give a history of oral symptoms like oral irritation, throat tightness, lips, oral and throat swelling, oral mucosal blebs. These local symptoms quickly disappear and are not particularly serious, but they may proceed to urticaria, asthma, abdominal pain. Severe forms of OAS may resemble or precede food-induced anaphylaxis (which suggested the term ‘oral allergy syndrome’). Thus, detection and recognition of OAS is important. OAS diagnosis is based on the patient's history and RAST. Treatment of OAS includes food avoidance, drugs and specific immunotherapy. Patients with pollen allergy should be informed about the possibility of hypersensitivity to certain fruits and vegetables.

**Delusion of Parasitosis**—It is a rare psychiatric disorder in which the patient has a fixed, false belief that he or she is infested by bugs, mites, worms, parasites or other living creatures. Even though it is a psychiatric disorder, these patients usually present to a dermatologist because they are convinced that they have a dermatological problem. Patients with delusions of parasitosis generally reject psychiatric referral. The diagnosis of delusions of parasitosis can often be made on the basis of the history alone; however, these beliefs may be brought about by drug use, or abuse, CVD, neurosyphilis, schizophrenia, psychotic depression, hypochondriasis, or an obsessional fear that parasites are present in the body. Therefore, it is important to make sure that the patient does not have an organic skin disorder, and the delusion is not secondary to another mental or physical illness.



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## CHAPTER

# 36

## Red Eye

### SYNOPSIS

The common term *red eye*, which is due to hyperemia or engorgement of the superficial visible conjunctival, episcleral, or ciliary vessels, is applied to a variety of distinct infections and inflammatory disease processes that involve one or more tissue layers of the eye, i.e. eyelids, conjunctiva, cornea, sclera, and uveal tract.

Most cases are due to benign or self-limiting conditions; however, several signs and symptoms may herald a serious ocular disorder, and a few are vision-threatening, and can lead to permanent vision loss, e.g. corneal ulceration and acute glaucoma. “The emergency physician must be adept at recognizing *red flags* from the history and physical examination that necessitate immediate treatment and referral. In addition, it is imperative for the emergency physician to recognize the need for immediate versus elective ophthalmologist consultation for the various conditions.”<sup>1</sup>

### DIFFERENTIAL DIAGNOSIS

#### Common

- Conjunctivitis (viral, bacterial, allergic, and Keyboard conjunctivitis): *vide infra* (↓↓).<sup>2-4</sup>

- Epidemic keratoconjunctivitis (EKC)\*
- Blepharitis
- Pingueculitis
- Pterygium
- Corneal abrasion<sup>†</sup>
- Superficial foreign body.

#### Occasional

- Acute angle closure glaucoma (AACG)
- Scleritis/episcleritis
- Keratitis (corneal infection, corneal ulcer)
- Iritis (anterior uveitis)
- Orbital cellulitis (due to paranasal sinusitis, infected tooth)<sup>5</sup>
- Trauma (contusion; penetrating wounds; burns—arc eye, chemicals)
- Subconjunctival hemorrhage (blood dyscrasias; systemic febrile disease: Measles, falciparum malaria, leptospirosis)
- Cluster headache (migrainous neuralgia).

\*The most commonly associated serotypes include adenovirus 8, 19, and 37.

<sup>†</sup>Corneal abrasions, i.e. superficial or partial trauma to corneal epithelium; often caused by fingernails, makeup applicators, dust, and vegetative matter.

**Rare**

- Keratoconjunctivitis sicca (old age; Seronegative spondyloarthropathies; Sjögren's syndrome; medications—anticholinergics, antihistamines, antidepressants)
- Thyrotoxicosis (Graves' disease)
- Granulomatous disease (TB, sarcoid)
- Spirochetal disease (syphilis, Lyme disease)
- Orbital vascular tumors (cavernous hemangiomas, carotid-cavernous sinus fistula, meningiomas, arteriovenous malformation).

**INVESTIGATIONS—GENERAL****ESR**

- Elevated significantly in inflammatory and autoimmune disorders, e.g. scleritis, uveitis.

**Blood Glucose**

- To detect diabetes and to monitor blood glucose, especially in nonhealing corneal ulcers.

**INVESTIGATIONS—SPECIFIC****Gram's Stain of Conjunctival Exudates**

- May show predominant polymorphs and bacteria in bacterial conjunctivitis; lymphocytes in viral conjunctivitis; and eosinophils in allergic conjunctivitis.

**Culture of Exudate**

- Especially in corneal disease and in cases that are resistant to therapy.

**Immunofluorescent PCR Tests**

- For *Chlamydia* and herpes-specific antigen, especially in posterior uveitis.

**Orbital US**

- Red eye *per se* does not warrant US; but in patients suspected with retinal detachment,

vitreous hemorrhage, intraocular foreign bodies, orbital tumors and trauma, high resolution ultrasound examination is found to be a safe, noninvasive, inexpensive, atraumatic and accurate means of evaluating the eye.<sup>6</sup>

**Orbital CT Scan**

- In orbital trauma, to rule out fracture of orbital bones; or associated with intracerebral, or subarachnoid hemorrhage.

**RF, ANA**

- To screen for autoimmune diseases (RA, Sjögren syndrome, uveitis).

**HLA-B27**

- If iritis/uveitis is suspected—to find the underlying cause, e.g. HLA-B 27 typing for ankylosing spondylitis.

**Syphilis Serology**

- VDRL, fluorescent treponemal antibody absorption (FTA-ABS) test in cases with scleritis, and posterior uveitis.

**CLINICAL NOTES**

- History should focus on:
  - *Onset*—Conjunctivitis generally has rapid onset (within hours), while a small FB will produce a sudden hyperemia within minutes. Abrupt onset with copious purulent discharge in a sexually active patient is typical of *hyperacute bacterial conjunctivitis*, which is most often associated with *N. gonorrhoeae*.
  - *Pain and photophobia*—A patient with conjunctivitis may complain of mild irritation and has normal light sensitivity. Their presence indicates serious under-

- lying disease process, including keratitis, glaucoma, uveitis, and orbital cellulitis.
- *Discharge*—Patients will often complain that their lids are stuck together in the morning when they wake up. It is typically due to matting of eyelashes on the discharge, and does not occur in iridocyclitis or glaucoma. A corneal ulcer may also be accompanied by exudation. The type of ocular discharge may be helpful to determine the cause of conjunctival inflammation; e.g. profuse purulent discharge is typical of *N. gonorrhoeae* infection; a mucopurulent or purulent discharge suggests a bacterial infection; a serous, ropy (i.e. sticky thread-like) discharge is most commonly associated with viral or allergic ocular conditions.
  - *Itching*—Usually indicates an allergic conjunctivitis.
  - *Unilateral or bilateral*—Conjunctivitis, though initially present in one eye, the second eye becomes involved a few days later. However, chronic unilateral or bilateral conjunctivitis (or red eye) may be due to meibomianitis or less common entities, e.g. occult FB, keratitis, nasolacrimal duct obstruction, or conjunctival neoplasm.
  - *Visual changes*—Do not rely on patient's subjective assessment of blurring of vision. Blurred vision (BV) often indicates serious ocular disease, e.g. AACG. BV that improves with blinking suggests a discharge or mucus on the ocular surface; otherwise, it's prudent to check the visual acuity (VA) using Snellen's chart and pin hole card.
  - *Colored halos*—Rainbow as fringes or colored halos seen around the point of light are a danger symptom suggesting AACG as a cause of the red eye.
  - *Ocular trauma*—Any conjunctival and corneal abrasion, contusion, and FB are important causes of red eye.
  - *Contact lens use*—They are prone to cause infection or the *contact lens-induced acute red eye* (CLARE: vide infra ↓↓) or *overwear syndrome*.
  - Sexual history and history of urethral discharge—It must be elicited in suspected gonococcal infection; it is important to ask about sexual contacts as this is a highly contagious infection. Prompt investigation must be ensured, which if left unnoticed, could subject the patients to a great deal of anxiety and distress
  - Associated systemic problems may be helpful to determine the possible cause; e.g. recent URTI or history of atopy (viral conjunctivitis); diabetes/hypertension (subconjunctival hemorrhage, glaucoma); thyrotoxicosis, rheumatoid arthritis and other autoimmune diseases (keratoconjunctivitis sicca, scleritis)
  - Topical medications, i.e. conjunctivitis medicamentosa, due to antiglaucoma drugs, gentamicin, topical vasoconstrictors (rebound hyperemia), topical drugs with preservatives, artificial tears; and systemic drugs, e.g. antiplatelet/antithrombotic agents, etc. can cause red eye
  - The basic examination should include:
    - *Visual acuity*—VA must be recorded with every patient with an eye involvement. It is usually normal in conjunctivitis unless cornea is involved and in AACG, and uveitis.
    - *Eyelids*—Inflamed in blepharitis, FB under the eyelid.
    - *Conjunctiva*—For the nature and location of hyperemia.
    - Pupillary abnormalities and corneal opacities are explained in Table 36.1.

Table 36.1: Red eye—Differential diagnosis

Disease	Distribution of redness/pain	Vision/photophobia	Corneal surface	Pupil	IOP
Acute conjunctivitis	Peripheral, diffuse, with irritation	Normal, no photophobia	Normal	Normal	Normal
Scleritis / episcleritis	Segmental, often around cornea; aching pain, tenderness	Normal, no photophobia	Normal	Normal	Normal
Acute iritis	Maximum around cornea; painful with radiation to brow, temple, nose.	Blurred, with photophobia	Dull	Constricted, irregular; may be no light reflex	Normal or low
Acute glaucoma	Mainly circumcorneal, severely painful with nausea, vomiting	Markedly blurred, halos around light, with photophobia	Hazy, dull	Mid-dilated, fixed, no light reflex	Elevated
Corneal ulcer	Mainly circumcorneal; painful	Usually, blurred, with photophobia	Dull, fluorescein dye stains ulcer	Normal	Normal
Subconjunctival hemorrhage	Localized; painless	Normal, no photophobia	Normal	Normal	Normal
Herpes simplex keratitis	Unilateral, circumcorneal, Dendritic ulcer	Blurred but variable; with photophobia	Abnormal	Normal	Normal

- *IOP (tonometry)*—Elevated in acute glaucoma (normal IOP- 10-21 mm Hg).
- *Slit-lamp examination*—To detect corneal and ocular FBs.
- *Fluorescein dye test*—Every patient with conjunctivitis should have fluorescein staining in each eye to ensure that a corneal aberration, ulcer, or herpetic dendrites is not missed.
- *Direct ophthalmoscopy*—When performed from a distance of 15 cm, can detect opacities in the cornea, lens, and vitreous. The fundus and optic disc, looking for increase in the cup-disc ratio, which may signify presence of acute glaucoma, can also be evaluated.
- Periauricular lymph nodes may be palpable in viral, chlamydial conjunctivitis, and acute gonococcal infection.
- Recurrent subconjunctival hemorrhage with no known cause, a work-up for hematologic disorder is indicated.
- A gritty sensation is common in conjunctivitis, but the presence of FB must be excluded.
- Hyperacute bacterial conjunctivitis needs emergent referral to prevent corneal involvement, including perforation and visual loss, which could also be due to therapeutic misadventure with topical steroid usage. Therefore, it's prudent to refrain from treating any patients with steroids without consultation.
- Beware of allergy or toxicity to topical medications, i.e. iatrogenic, (including cosmetics) as a cause of persisting symptoms.
- Never use mydriatics when examining red eye—acute glaucoma may be precipitated; they also act as temporary decongestants, and mask hyperemia.
- Syphilis—It being a multisystem, multi-symptom disorder is a great mimic. Therefore, it is important to always keep this condition in mind when encountering patients with

## RED FLAGS

- All patients with severe eye pain (suggesting increased IOP), photophobia, and corneal haziness require immediate ophthalmic referral.
- In a patient with acute onset, unilateral headache, vomiting, acutely painful eye, or

anterior uveitis, chorioretinitis, retinal vascular occlusion, and chronic anterior segment inflammation.<sup>7</sup> Further manifestations of syphilis can be complicated by concurrent HIV infection; hence, always consider HIV infection, e.g. CMV retinitis and Kaposi's sarcoma in patients with syphilis.

## SELECTED GLOSSARY

**Contact lens-induced acute red eye (CLARE)<sup>8</sup>**—Contact lenses offer a unique and viable mode of visual correction and are also of therapeutic value in a range of ocular disorders. However, several reports in the literature have clearly shown that contact lens wear is not totally compatible with ocular physiology, and is associated with various complications. Evidence also suggests that an increased number of these complications are seen with hydrogel lenses used on an over-extended contact lens wearing time or improperly used contact lenses in a closed eye environment (during sleep). Some of these conditions include inflammatory responses such as Contact Lens Induced Acute Red Eye (CLARE), and Culture Negative peripheral Ulcers (CNPU), and sight threatening responses such as infectious keratitis. While the etiology of a CLARE response is not clearly understood, it is seen that the condition is distinct and typically presents with the patient waking in the early hours with discomfort and pain in the involved eye. Other symptoms include an intolerance to lens wear associated with redness, lid swelling and mild to moderate amount of photophobia. Clinical signs include severe bulbar and limbal injection, and the presence of diffuse subepithelial to anterior stromal infiltration in the periphery of the cornea. Most often the presentation is unilateral and epithelial involvement is usually minimal. Further, patient who has endured an episode is susceptible to

repeat occurrences. Patient who have had a CLARE should be educated and fitted with daily wear lenses.

**Keyboard conjunctivitis**—An inconspicuous way of spread of conjunctivitis—by the use of *keyboards of shared computers*, at places like a library, internet café, classrooms, etc. Shared keyboards and mouse are usually the culprits. Transmission of conjunctivitis is nearly certain, if a patient with conjunctivitis/ carrier used the same keyboard earlier. Other examples of conjunctivitis (i.e. red eye) due to fomite transmission include objects such as mobile phones, land phones, TV remote tools, fridge or door handles, contaminated vehicles, shovels, clothing, bowls/buckets, brushes, tack, and clippers. Symptoms of conjunctivitis usually start within a day or two.

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## CHAPTER

# 37

## Sexual Dysfunction

### SYNOPSIS

*Sexual dysfunction*<sup>\*</sup>, in either sex, is often the result of a complicated interaction of biological, psychological, and interpersonal difficulties between sexual partners, and may be defined as a consistent long-term inability to respond in a way that characterize the normal sexual response cycle.

The *normal* sexual response cycle, as classified by DSM-IV-TR system, comprises four phases:

1. Desire—Fantasies and desire about sex activity,
2. Arousal—Pleasure and physiological response,
3. Orgasmic—Release of sexual tension and rhythmic bodily response, and
4. Resolution—General relaxation and well being; the anatomic structures involved in sexual response return to a baseline state.

The DSM-IV-TR system specifies three *criteria* which are essential during the process of evaluation for sexual dysfunction. They are:

1. Symptoms have to be recurrent or persistent,
2. Cause marked distress or interpersonal difficulty, and

3. Cannot be accounted by another Axis I (i.e. clinical syndrome) disorder or substance effect.

Based on these criteria, the common sexual dysfunctions as classified by DSM-IV-TR may be grouped as follows (Table 37.1):

- In men:
- Erectile dysfunction (ED: *vide infra* ↓↓),
  - Premature ejaculation (PE: *vide infra* ↓↓),
  - Retarded ejaculation, and
  - Retrograde ejaculation (*vide infra* ↓↓).
- In women:-
- Frigidity (i.e. female sexual arousal disorder—FSAD: *vide infra* ↓↓),
  - Orgasmic dysfunction (*vide infra* ↓↓), and
  - Vaginismus (*vide infra* ↓↓).
- In both:
- Dyspareunia (*vide infra* ↓↓),
  - Low libido (i.e. hypoactive sexual desire disorder—HSDD), and
  - Sex aversion disorder.

Sexual dysfunction can be *primary* (meaning lifelong or never normal before), *secondary* (meaning acquired with normal function before), *selective* (such as only with a particular

<sup>\*</sup> Sexual dysfunction due to gender identity, homosexuality, and paraphilias is not discussed.

**Table 37.1:** Classification of sexual dysfunction

Disorder	Male	Female
• Sexual desire disorder	• Alibido/low libido/sexual phobia/aversion	• Alibido/low libido/sexual phobia/aversion
• Sexual arousal disorder	• Erectile dysfunction	• Failure of arousal (absence of vaginal lubrication)
• Orgasmic disorder	• Premature ejaculation / Retarded ejaculation	• Anorgasmia
• Sexual pain disorder	• Painful ejaculation/ Dyspareunia	• Vaginismus/ Dyspareunia

partner), *generalized* (due to complex, deep rooted causes), or due to combined factors.

Since sexual dysfunction is quite common, but not obvious, it is essential that physicians assume a proactive role. Every effort should be made to differentiate between psychogenic/functional and organic sexual dysfunction, assessed via standard questionnaires such as the International Index of Erectile Function and Female Sexual Function Index (see below). In an obvious psychogenic case, expensive and time-consuming investigations should be avoided. However, if an organic cause is suspected to be the basis of sexual dysfunction, every effort should be made to discern that organic cause as early as possible, and refer to the appropriate specialist for further investigations and management.

## DIFFERENTIAL DIAGNOSIS (TABLE 37.2)

### Common

- Psychogenic factors:
  - Personal problems (young men-new partner, anxiety, depression)
  - Relationship problems (poor communication, unresolved conflicts, lost trust, Widower's syndrome: *vide infra* ↓↓)
  - Psychosexual problems (sexual performance anxiety, prior sexual failure, negative learning and attitude about sex)

**Table 37.2:** Common conditions and agents affecting sexual function

### Psychosocial

- *Psychiatric*: Anxiety, depression, PTSD
- *Psychosocial*: Ignorance, poor relationship, poor sexual drive, performance anxiety, prior sexual failure, negative attitude

### Medical

- *Cardiovascular*: Angina, previous MI
- *Respiratory*: Asthma, COPD
- *Endocrine*: Diabetes mellitus, hypothyroidism, hyperthyroidism
- *Metabolic*: Atherosclerosis, hepatic failure, renal failure
- *Neurological*: Stroke, peripheral neuropathy, spinal cord disorders
- *Gynecological*: Vaginitis, PID, endometriosis, fibroid, postmenopausal vaginal atrophy
- *Arthritic*: Arthritis from any cause
- *STD*: herpes, gonorrhea
- *Aging*: Andropause, menopause

### Surgical

- Phimosis, hydrocele, episiotomy scarring, prostatectomy, mastectomy (poor body image), oophorectomy, colostomy, amputation

### Drugs

- *Prescribed*: Antihypertensives, antidepressants, antipsychotics, mood regulators, antihistamines, hypnotics, sedatives, hormones, anabolic steroids, corticosteroids
- *Substance abuse*: Alcohol, opium, cocaine, barbiturates

### Genetic

- Peyronie's disease

- Post-traumatic stress disorder (PTSD: *vide infra* ↓↓)
- Sexual enactment factors (lack of penile/vaginal stimulation, lubrication; unfavorable sexual positions)
- Genital (phimosis)
- Endocrine (diabetes mellitus, hypothyroidism, thyrotoxicosis)
- Cardiac (hypertension, CAD)
- Metabolic (atherosclerosis, dyslipidemia, obesity)
- Medications (antihypertensives, antidepressants, anxiolytics, etc.)
- Substance abuse (alcohol, tobacco, opioids, cocaine)
- Pregnancy (especially in the first and last trimester)
- Aging/postmenopausal.

### Occasional

- Vaginal/pelvic disorders (infection—vaginitis, PID; fibroid, tumor; childbirth injury)
- Neurogenic (stroke)
- Postsurgical (prostatectomy, pelvic adhesive disease).

### Rare

- Neurogenic (brain tumor, spinal injury/compression)
- Endocrine (prolactinoma, Addison's disease, hypogonadism)
- Vascular occlusive disease (Leriche' syndrome: *vide infra* ↓↓)
- Congenital disease/malformation (Peyronie's disease: *vide infra* ↓↓)
- Genital trauma.

## INVESTIGATIONS—GENERAL

### Blood Glucose

- Diabetes mellitus is a common cause of ED. Present evidence supports ED as a significant marker for diabetes, particularly in younger patients. Men 45 years old or younger with ED were more than twice as likely to have diabetes mellitus as men without ED, and men with ED 46 to 65 years old were likely to have diabetes. Thus, markers of ED may represent an early warning for the development of diabetes, which is particularly important considering many diabetic patients remain undiagnosed for several years. Therefore, fasting, two hour postprandial blood glucose, and HbA1c estimation should be obtained.<sup>1-3</sup>

### Lipid Profile

- Hyperlipidemia, along with hypertension and diabetes mellitus, is a risk factor for metabolic syndrome which often coexists with ED; therefore its estimation is important.<sup>4,5</sup>

### TFTs

- Elevated TSH with diminished FT4 values in primary hypothyroidism, and subnormal/undetected TSH levels with elevated T3 or T4 or both in thyrotoxicosis
- TFTs are also useful to discover subclinical hyperthyroidism (T3, T4 normal, TSH undetected); and subclinical hypothyroidism (T4 normal, TSH raised) which may be responsible for sexual dysfunction.

### Chemistry Panel

- LFTs, urea, creatinine, and VDRL as indicated.

### Serum Testosterone-free (AM Sample)

- Low levels in patients with diminished libido, or any signs of diminished secondary sexual characteristics, i.e. mild or otherwise asymptomatic androgen deficiency, or hypogonadism.

### Microscopy/Culture

- Vaginal secretions (vaginitis, gonococcal); prostate (prostatitis).

## INVESTIGATIONS—SPECIFIC

### Serum Prolactin (PRL)

- If serum testosterone levels are low, serum PRL should be measured. High (>20 ng/ml) levels—either due to hypothalamic-pituitary lesion (suppressing GnRH) or drug induced—are observed in patients with low libido, in women with little or no history of menstruation, and gynecomastia.

### LH and FSH

- Serum LH and FSH estimation helps to differentiate the etiology of sexual dysfunction,

either due to testicular (Leydig cell) failure or hypothalamic-pituitary lesion.

- If LH and FSH are normal or low, and PRL is also normal, then the diagnosis is hypothalamic-pituitary lesion.
- If LH and FSH are high, and PRL is normal, then the diagnosis is testicular (Leydig cell) failure.
- If LH and FSH are low, but PRL is high, pituitary adenoma needs to be ruled out.

#### Nocturnal Penile Tumescence (NPT)

- Penile erections during REM sleep support psychogenic etiology, and eliminate significant neurologic, vascular, or endocrine causes of ED.

#### Intracavernosal Injection and Sexual Stimulation

- To assess penile vascular function.

#### Penile Duplex US

- To evaluate vascular function within the penis, i.e. in the cavernous arteries, before and after injection of a vasodilator such as prostaglandin E1, e.g. in Peyronie's disease. Duplex US can also evaluate blood flow velocities to the clitoris, labia, urethra, and vagina.

#### Perineal and Clitoral Electromyography

- To detect sensory neuropathy in pudendal nerve pathway, and in evaluating the autonomic innervation of the clitoris due to diabetes mellitus and alcoholism.

#### Pelvic Arteriography

- In young men with arterial insufficiency as the cause for their ED, and who are candidates for reconstructive surgery.

#### US Testis and Pelvis

- To assess testicle/epididymis size, enlargement, growth, congenital abnormality, and adnexal, uterine lesions.

#### CT/MRI Scan

- As indicated in patients with pituitary adenoma (hyperprolactinemia with normal LH, FSH).

#### CLINICAL NOTES

- Detection of sexual dysfunction in a patient or a couple depends upon asking appropriate questions because many are reluctant to initiate discussion of their sex lives. Further, what is regarded as normal sexual function, and therefore, what is thought to be impaired or unsatisfactory sexual performance depends in part on the expectations of the couple concerned. For example, one couple may regard it as normal that the woman is regularly unable to achieve orgasm, whilst another may seek treatment. It is also a fact that many physicians have their own inhibitions in taking detailed sexual history from the patient. Some of the potential barriers cited for reluctance to address sexual health issues include: embarrassment, feeling ill-equipped or inadequate training to elicit sexual history, belief that sexual history is not relevant to the chief complaint, and time constraints.<sup>6,7</sup> Thus both patients and physicians need to curtail their inhibitions, and begin to take the first steps toward better sexual communication
- Patients prefer to communicate their symptoms related to sexual dysfunction in the privacy of verbal communication with their physician. A respectful, open-minded, and relaxed approach is essential. Questions should be asked in a matter-of-fact, yet

sensitive manner, avoiding jargon. A simple way to do this is by simply asking, “how are things going for you sexually?”, or, “how is your sex life? Is everything all right?”; this type of inquiry should elicit a clear, quick, and direct response such as “everything is fine.” Any other answer may suggest potential sexual dysfunction in him or her which should be followed up (with consent) with specific questions to identify problems associated with various phases of sexual response cycle (see above). If the patient is part of the couple, the couple should be interviewed together

- It is not unusual for some patient to be unaware of an association between their medical problem and underlying sexual dysfunction. For example, patients with obesity, tension headache, chronic backache, vaginal discharge, pelvic pain, etc. This is an opportunity for the physician to recognize such an association and tactfully include inquiry about sexual dysfunction
- A two way approach may be adopted in obtaining sexual dysfunction history: The *screening* method and the *in-depth* approach. If the sexual history seems unrelated to the chief complaint, a few screening questions will suffice. Questionnaires have been developed to collect data regarding ED (International Index of Erectile Function — IIEF<sup>†</sup> and female sexual dysfunction (Female Sexual Function Index — FSFI<sup>‡</sup>) to assess the severity and impact of therapy in such patients which may be useful to understand the nature and scope of the patient’s problem. If the complaints have direct bearing to the chief complaints, a more

detailed, i.e. in-depth sexual history is needed<sup>8</sup>

- Loss of NPT—At the very beginning a carefully taken sexual history helps to rule out organic causes of sexual dysfunction, especially treatable ones. An alerting sign is a loss of male morning erection, i.e. loss of NPT during REM sleep. A history of erection that occurs nocturnally, during masturbation, or during foreplay, or with other sexual partners eliminates significantly neurologic, vascular, or endocrine cause of ED. For women there can be a similar loss of nocturnal vaginal lubrication
- Hidden agenda—Although some patients may present directly with a complaint of sexual dysfunction, many will present with unexpected add-on problem at the end of consultation as hidden agenda or *exit problem* or *parting shot*. The exit problem or parting shot is usually the patient’s main reason for consultation. Examples wherein such situation is commonly encountered are:
  - Sexual inquiry as part of current illness management
  - Sexual inquiry as part of health check-up
  - Premarital sexual concerns
  - Important life events, e.g. marriage
  - Exposure to STD
  - Medication side-effects
  - Infertility, menopause, andropause.
- Despite a seemingly indirect or ‘by-the-way’ nature of such encounters, the issue must be recognized and treated with considerable importance
- History—Includes age, mode of onset, duration, libido (i.e. sex drive), situational context, foreplay, fantasies, frequency, erection, orgasm, ejaculation (normal, premature, delayed, or absent), and pain felt during intercourse

<sup>†</sup> Web site: <<http://www.urologyspecialists.net/print/iief.html>>Accessed on 16-11-08

<sup>‡</sup>web site:<<http://www.fsfiquestionnaire.com/FSFI%20questionnaire2000.pdf>>Accessed on 16-11-08

- Sexual history—Includes early experiences (sexual abuse), sexual knowledge, attitude towards sexuality, past sexual practices, current sexual relationship, self-pleasuring practices and fantasies, homosexual experiences, personal body image, and any past negative sexual experiences such as sexual assault, incest
- Stress—Current stress factors such as interfamily problems with children, elders, death, and extrafamilial factors such as stress from occupation, legal, and financial matters create problems in the sexual relationship
- Habits—Such as nicotine use, alcohol intake, and illicit drug use should be documented
- Medication history—Important in all individuals with sexual dysfunction. The onset, frequency, and duration of the sexual side effects of drugs are variable, which can be confirmed by 'drug holiday'
- Mental state examination—May be indicated to exclude psychiatric disorders and to explore guilt, shame, anger and other emotional elements associated with sexual dysfunction
- Family history—Includes parental influences, cultural and religious influences, family violence, and relationship with siblings
- Past history—Any disease, injury, or surgery that could affect sexual functioning
- Table 37.3 briefly states historical features for the assessment of sexual dysfunction mentioned above
- Vasculopathy has come to be recognized as the most common cause of ED, which has elevated ED's importance in the primary care setting as a sentinel to underlying cardiovascular disease. Identification of cardiovascular risk factors should be a routine part of the evaluation for ED, and is as important as taking the patient's sexual, medication, and psychosocial histories<sup>9</sup>
- Physical examination—The important basic aspects include:

**Table 37.3:** Assessment of historical features for sexual dysfunction

- Define the problem—As it appears to each partner, in their own words
  - Onset, course—Always a problem, or after a period of normal functioning
  - Any other partner—Sexual functioning in other context, problem confined to one or other partner, elicit history individually
  - Sexual drive—Early morning or nocturnal penile erection, sexual thoughts /feelings of sexual arousal, masturbation, frequency of intercourse
  - Knowledge and fears—Misconceptions, religious belief, strict religious upbringing sex education, sexual techniques
  - Interpersonal relationship—Either partner shy, low self-esteem, aggressive, marital conflicts
  - Psychiatric disorder—Especially depression, guilt about sexual impulses, PTSD
  - Substance abuse—Alcohol, drugs
  - Associated illness—Medical or surgical
  - Reason for present consultation—To elicit history of any recent adverse psychosocial developments, biological factors such as newly diagnosed disease or surgical intervention
- 
- General—Secondary sex characteristics.
    - Gynecomastia in men (hepatic cirrhosis, digoxin, spironolactone, testicular tumor, hypogonadism, Klinefelter's syndrome: *vide infra* ↓↓).
    - Galactorrhea in women (pregnancy, drugs, hypothyroidism, hyperprolactinemia).
    - Blood pressure, peripheral pulses, xanthelasma.
    - Thyroid (goiter, nodules), chest, and abdomen.
  - Neurologic:
    - Sensation, tendon reflexes (peripheral neuropathy).
    - Anal sphincter tone (inconsonance, pelvic floor childbirth injury).
    - Bulbocavernous reflex (lower motor neuron lesion).
  - Male:
    - Penis (malformation, discharge, ulcer).
    - Scrotum, testis, epididymis (cryptorchism: *vide infra* ↓↓).



- Rectal examination (fissure, hemorrhoids, prostate).
- Female:
  - External genitalia (inflammation).
  - Introitus (intact hymen, remnants of hymenal ring, rigidity).
  - Vagina (atrophy, discharge stenosis).
- Pelvic examination (adnexal mass, PID).
- Rectal examination (as above).

### RED FLAGS

- Avoid moral or religious judgement of patient's behaviour. Respect patient's reluctance to disclose all sexual and relationship details, especially during the initial discussion.

### SELECTIVE GLOSSARY

**Cryptorchism (or Cryptorchidism)**—It is defined as failure of the testis to descend from its intra-abdominal location into the scrotum. The exact etiology of cryptorchidism is not known. It usually presents at birth or by preadolescence; however, it can present at any age. In one-third of patients, the condition is bilateral. Patients present with the condition or the parents bring the child with nonpalpable testis. Physical examination reveals a nonpalpable testis in the scrotum. The most common location of the cryptorchid testis is in the inguinal canal (72%), followed by prescrotal (20%) and abdominal (8%) locations. US, CT, MRI, arteriography, and laparoscopy are used for diagnosis. Testicular malignancies occur in 10% of men with cryptorchid testis. The primary treatment of cryptorchid testis is orchiopexy.

**Dyspareunia**—Persistent or recurrent genital pain, during or after sexual intercourse, in either sex; much more common in women, and uncommon in men (usually organic in men, e.g. Peyronie disease).

**Erectile dysfunction (ED)**—Persistent or recurrent partial or complete failure to attain or maintain erection until completion of sexual activity. ED becomes more common with age, but is not part of the normal aging process. ED is a symptom of other potentially serious medical conditions. It may indicate incipient cardiovascular disease, neurologic degeneration, hormonal imbalances, psychological issues, and even marital problems. Therefore, it's important to perform basic physical and psychological evaluation of the patient and evaluate the risk factors for any impending disease.

**Female sexual arousal disorder (FSAD)**—Persistent or recurrent inability to achieve or maintain sufficient sexual excitement, expressed as a lack of excitement or a lack of genital or other somatic responses such as adequate lubrication-swelling response of sexual excitement. It's usually due to psychological conflicts; altered hormonal balance (testosterone, estrogen, prolactin, and thyroxin); may be associated with depression or medication effect. However, a detail history is essential to rule out inadequate, focussed, sexual stimulation and duration of sexual activity.

**Hypoactive sexual desire disorder (HSDD)**—It is the persistent or recurrent deficiency (or absence) of sexual fantasies or thoughts and/or the lack of receptivity to sexual activity. It's usually due to reaction to sexual dysfunction, chronic illness, surgery, major depression, chronic anxiety, and marital discord, hyperprolactinemia, or CNS depressants.

**Klinefelter's syndrome**—KS, 47, XXY and its variants, is the most common chromosomal aberration among men, associated with hypogonadism (small testes, azoospermia/oligospermia), gynecomastia in late puberty, and infertility. Sexual dysfunction symptoms include erectile dysfunction, and subnormal libido. Other

symptoms include fatigue, weakness, osteoporosis, language impairment, academic difficulty, and psychiatric disorders involving anxiety, depression, neurosis, and psychosis. Infertility and gynecomastia are the two most common symptoms that lead to diagnosis, but many cases of KS remain undiagnosed because of substantial variation in clinical presentation. MRI brain findings indicate a reduction in left temporal lobe gray matter, a finding that is consistent with the verbal and language deficits associated with KS. Chromosomal studies are indicated in prepubertal males with low testosterone and elevated FSH and LH levels to assess for Klinefelter syndrome. A semen analysis (as per the WHO guidelines) is indicated if fertility is an issue.

**Leriche syndrome**—It is used to describe chronic lower limb ischemia characterized by: Intermittent claudication in the buttocks; pale, cold legs; sexual impotence; and absent femoral pulses. It is caused by aortoiliac obstruction (e.g. saddle embolism at bifurcation of the aorta). The vessels above and below may be relatively normal.

**Orgasmic dysfunction**—It is also called inhibited male/female orgasm or retarded ejaculation of the male; wherein there is persistent or recurrent delay in, or absence of orgasm following a normal arousal phase during sexual activity—the individual may be sexually aroused but orgasm is impaired or absent.

**Peyronie's disease** (*synonyms: Penile fibrosis, Induratio penis plastica*)—A condition characterized by hardening of the penis due to the formation of fibrous plaques on the dorsolateral aspect of the penis, usually involving the membrane (tunica albuginea) surrounding the erectile tissue (corpus cavernosum penis). This may eventually cause a painful deformity of the shaft or constriction of the urethra, or both, leading

to penile angulation or an hour-glass like deformity with distal flaccidity. It usually affects only the erect penis. Sexual intercourse can become painfully difficult or impossible. Genetic susceptibility is thought to play a role. Penile X-ray and ultrasound can demonstrate calcified and noncalcified plaques respectively. Corpus cavernosography can help to demonstrate cavernosus deformity and vascular blockage.

**Post-traumatic stress disorder (PTSD)**—PTSD is a psychological condition that is triggered by experiencing or witnessing severe trauma that constitutes a threat to the physical integrity or life of the individual or of another person; these events being extreme in nature, not necessarily outside the normal range of human experience, but such as to arouse intense fear, helplessness or horror, e.g. natural disasters, violent personal assaults, rape, war, severe automobile accidents, or the diagnosis of a life-threatening condition. Sexual assault on women probably is the most important cause of PTSD. Four categories of criteria are needed to accurately diagnose PTSD.

- First, a traumatic event occurred in which the person witnessed or experienced actual or threatened death or serious injury, and responded with intense fear, horror or helplessness.
- Second, on exposure to memory cues, the person has reexperiencing symptoms, such as intrusive recollections, nightmares, flashbacks or psychologic distress.
- Third, the patient avoids trauma-related stimuli (avoid thoughts, feelings, conversations, places or people that arouse recollections of trauma), and feels emotionally numb.
- Fourth, the person has increased CNS arousal, manifested by difficulty falling or staying asleep, irritability or outburst of anger, difficulty concentrating, hypervigilance, and startle response.

The symptoms persist for at least one month and significantly disturb the patient's social or occupational functioning (or both). Acute PTSD is diagnosed when the symptoms have lasted for 1-3 months as against chronic PTSD, where symptoms have lasted for more than 3 months. The importance of this distinction lies in the fact that active treatment in acute PTSD may reduce the high risk of developing chronic PTSD. Although level of exposure to traumatic stressor is directly related to the psychological impact, other factors contribute to development of PTSD. Thus history of previous panic disorders, previous trauma, child abuse, drug abuse, as well as socioeconomic and demographic factors and ethnicity, appear to be risk factors for vulnerability to PTSD.<sup>10,11</sup>

**Premature ejaculation (PE)**—Persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the person wished it (taking into account age, frequency, and situation); more common in younger men and often resolves with increasing experience.

**Retrograde ejaculation**—Sexual climax without the release of semen from the penis; occurs when the semen passes into the bladder rather than along the urethra. It is common after prostatectomy, neurologic disorder (Parkinson's disease, lumbar or sacral damage), and some antihypertensives (methyldopa).

**Sex aversion disorder**—Persistent or extreme aversion to and avoidance of all (or almost all) genital sexual contact with a sexual partner; applies mostly to female sex with history of sexual assault, severe negative self-esteem, marital discord, and in women complaining of gynecological symptoms, e.g. pelvic pain, vaginal bleeding, and other sexual dysfunctions.

**Vaginismus**—Persistent or recurrent involuntary muscle constrictions of outer third of vagina that prevents penile insertion and

intercourse (coitus), usually due to sexual trauma (rape, childhood sexual abuse); or as a consequence of dyspareunia, e.g. childbirth, surgery, gynecologic pathology, atrophic vaginitis; and also due to strict religious upbringing; or psychogenic factors.

**Widower's syndrome:** It refers to a male who experiences erectile dysfunction (with a new sex partner) secondary to guilt feelings relating to his dead spouse.

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## CHAPTER

# 38

## Sweating Abnormalities

### SYNOPSIS

Eccrine sweat glands are distributed all over the body surface,\* but are most dense on the forehead, palms and soles, and in the axillae. They open directly on the skin and their secretion, commonly called as 'sweat' (perspiration), is regulated by the body temperature center in the hypothalamus (the sudomotor system which controls sweat output) via the sympathetic cholinergic mediator. Any fluctuations in the sudomotor autonomic activity, consisting of frontal operculum,<sup>†</sup> hypothalamus, brainstem, spinal cord, sympathetic chain ganglia, peripheral nerve, or eccrine sweat glands may result in sweating abnormalities.

Sweating (i.e. insensible loss) is necessary to maintain body's normal thermoregulatory mechanism, and fluid and electrolyte hemostasis. The amount of sweat produced or its response to physiological stimuli of heat, emotion, or eating varies greatly by different individuals under various conditions, and therefore, it is difficult to define sweating abnormality—normal, excessive, or deficient—in an individual.<sup>1-3</sup>

Excessive sweating, called as *hyperhidrosis*, is sweating beyond what is necessary to maintain normal thermoregulation. Clinically, it may be defined as a condition where noticeable sweating occurs under different conditions, where it would not be normally expected to occur or occurs in excess,<sup>4</sup> often causing occupational disability and social embarrassment. Patients usually present because of abnormal wetness, sweaty palms, stained clothing, offensive odor, and change in the pattern of sweating. Patients report that they are even embarrassed to hold the hands of those they love.

*Hypohidrosis* and *anhidrosis* is reduced or complete absence of sweating respectively; the individual is unable to deliver sweat to the skin surface in the presence of appropriate stimuli.

The etiology of sweating abnormalities, i.e. hyperhidrosis and hypohidrosis, can be primary (idiopathic or essential) or secondary to a number of diseases and drugs. It may also be localized or generalized, although such a strict categorization may not be always possible in a clinical setting. Unilateral, transient (lasting 1 to 3 days) hyperhidrosis typically involving the face and arm have also been documented.<sup>5, 6</sup>

\* Except the nailbeds and some mucosal surfaces.

<sup>†</sup> Adjoining parts of the frontal, parietal and temporal lobes.

Whereas hyperhidrosis is usually benign, anhidrosis may predispose to hyperthermia. Either hyperhidrosis or anhidrosis may accompany a more serious underlying disorder. Correct diagnosis depends on determining the anatomical pattern of sweating and localizing the lesion within the autonomic nervous system.<sup>7</sup>

Sweating abnormalities, especially hyperhidrosis, can interfere with employment and social relationships, and cause immense anxiety to the suffering individual. Therefore, it is being recognized increasingly, and its treatment modalities are gaining widespread attention. However, in the majority of patients with hyperhidrosis, providing scientific explanation, and reassurance that excess sweating is not the consequence of pathological condition once medical causes have been ruled out is crucial in their symptomatic management.

## DIFFERENTIAL DIAGNOSIS

Can be considered separately for hyperhidrosis and hypohidrosis:

### A—Hyperhidrosis

#### Common

- Excessive exposure to heat, humidity, and vigorous exercise<sup>†</sup>
- Anxiety disorders<sup>§</sup>
- Infectious febrile diseases (typhoid, malaria, TB, HIV)
- Shock and syncope (myocardial ischemia, stroke, sepsis)
- Hypoglycemia
- Hyperthyroidism
- Menopause
- Gestatory hyperhidrosis (physiological—spicy food).

<sup>†</sup> Thermal sweating is governed by the hypothalamus.

<sup>§</sup> Emotional sweating is governed by the cerebral cortex.

#### Occasional

- Localized hyperhidrosis (palmoplantar, axillary, craniofacial)
- Alcohol and drug withdrawal
- Medications (antipyretics, insulin, venlafaxine, tricyclic antidepressants, pilocarpine, physostigmine)
- Other infections (endocarditis, brucellosis).

#### Rare

- Neoplasm (lymphoma, insulinoma, pheochromocytoma, carcinoid syndrome)
- Intrathoracic lesion (paroxysmal unilateral hyperhidrosis due to cervical rib, apical bronchial carcinoma)
- Neurologic diseases (hypothalamic lesions, Harlequin syndrome: *vide infra* ↓↓, autonomic dysfunction)
- Spinal cord lesions (posttraumatic syringomyelia)
- Endocrine (hyperpituitarism)
- Olfactory hyperhidrosis (facial sweating from perfume smell)
- Gestatory hyperhidrosis (pathological—Frey's syndrome: *vide infra* ↓↓)
- Poisoning (cholinesterase inhibitors, organophosphorus compounds)
- Familial (nail-patella syndrome: *vide infra* ↓↓)

### B—Hypohidrosis and Anhidrosis

#### Common

- Ductal obstruction (Miliaria, sweat retention syndrome, prickly heat)
- Systemic disorder (Heat stroke)
- Damage to sweat gland (scar, trauma, surgery, irradiation, scleroderma)

#### Occasional

- Local denervation (leprosy, xerotic dermatitis, segmental vitiligo)



- Medications (anticholinergics, antihistamines)
- Autonomic peripheral neuropathy (diabetes mellitus, uremia, alcoholic)
- Myxedema.

#### Rare

- Hypothermia
- Sjögren's syndrome
- Multiple system atrophy (MSA)<sup>8</sup>
- Congenital (hypohidrotic ectodermal dysplasia).

### INVESTIGATIONS—GENERAL

#### CBC

- Leukocytosis in bacterial infection, heat stroke; abnormal WBCs in leukemia; malarial parasites in malaria.

#### ESR

- Elevated in infection, malignancy, lymphoma, and autoimmune disease.

#### TFTs

- Elevated FT4 with low TSH suggest underlying hyperthyroidism or thyrotoxicosis; elevated TSH suggests hypothyroidism.

#### Blood Glucose

- May reveal diabetes mellitus or hypoglycemia. To confirm nocturnal hypoglycemia—in diabetic patients suspected with nocturnal sweating—blood glucose estimation around early hours of the morning must be done.

#### Urea, Electrolytes

- Elevated urea, creatinine and low sodium, potassium in heat stroke.

#### Purified Protein Derivative (PPD)

- To screen for TB.

#### HIV

- As indicated in immunodeficiency disorders.

#### CXR

- To rule out parenchymal lesions, tuberculosis, lymphoma, or a neoplasm.

### INVESTIGATIONS—SPECIFIC

#### Blood Culture

- In enteric fever, endocarditis, sepsis, and in infections due to immunodeficiency disease.

#### Iodine Starch Test

- Mapping out areas of excessive sweating, i.e. for direct visualization of the affected areas, may be done by the iodine starch test. The affected area is sprayed with a mixture of 0.5 to 1 gram of iodine crystals and 500 gram of soluble starch. Areas that produce sweat will turn black.

#### Urinary Catecholamines

- To rule out possible pheochromocytoma.

#### Urinary 5-Hydroxyindoleacetic Acid (5-HIAA)

- To screen patients suspected of carcinoid tumor; very high excretion rates of 5-HIAA occur in carcinoid syndrome.

#### Biopsy

- In patients with localized hyperhidrosis (e.g. focal axillary hyperhidrosis), eccrine nevus, eccrine angiomatous hemartoma, etc. biopsy is indicated.



## Sudomotor Testing<sup>9</sup>

- In rare disorders such as idiopathic hyperhidrosis, MSA, etc. sudomotor testing such as Quantitative Sudomotor Axon Reflex Test (QSART), Silastic sweat imprint test, and Thermoregulatory Sweat Test (TST) may be indicated. These tests have a high sensitivity and specificity for delineating the postganglionic sudomotor function and site of lesion.

## CLINICAL NOTES

- It is to be remembered that sweating varies with age because sweat glands function immaturely in infants and less active in elderly patients. As a result, patients in these age-groups may fail to display sweating associated with its common causes.
  - An important step in determining the cause of sweating abnormality is whether it is generalized or localized.
  - *Generalized hyperhidrosis* is common in adults and is usually secondary to severe physiologic stress (shock, pain); a metabolic disorder (diabetes mellitus, hypoglycemia, thyrotoxicosis, menopause, pheochromocytoma); febrile illness, drug effect, or malignancy. Therefore, it is essential to investigate for the underlying disorder.
  - *Localized hyperhidrosis* (palmoplantar, axillary, craniofacial) is often primary (idiopathic) and unlike generalized hyperhidrosis, usually begins in adolescence, but it can begin in childhood or even in infancy.
  - In generalized hyperhidrosis sweating is common during both waking and sleeping hours; whereas in local hyperhidrosis sweating usually reduces at night time and disappears during sleep.
  - History with regards to severity, extent, periodicity, duration, and its impact on the daily activities of the individual are noted.
- Excess sweating restricted to palms, soles, and axillae may be indicative of a normal response to everyday events, or if it is more generalized, may suggest an underlying medical disorder, commonly due to hyperthyroidism and menopause.
- If sweating occurs primarily at night (Table 38.1), then inquiry into fever, cough, expecto-ration, hemoptysis, weight loss, and other symptoms of esophageal reflux disorder and neoplasm should be sought. Tuberculosis, HIV infection, esophageal reflux, and menopause are known to be the most frequently associated disorders with *night sweats*, defined as “sweating at night even when it isn’t excessively hot in your bedroom within the previous month”.<sup>10</sup>
  - Paroxysms of sweating are common with anxiety disorders, menopause, carcinoid syndrome, and pheochromocytoma.
  - A drug history is inquired with a check for use of antipyretics, insulin, anticholinergics, antihistamines, and alcohol.
  - Physical examination—May include presence of weight loss (diabetes mellitus, hyperthyroidism; tachycardia (panic attack, hyperthyroidism, and heat stroke); hypotension (syncope, autonomic dysfunction); hypertension, facial flushing (pheochromocytoma, carcinoid syndrome); fever or defervescence.
  - The patient is examined for signs of other systemic disorders such as tuberculosis (segmental collapse, pleural effusion), hyperthyroidism (goiter, lid lag, exophthalmos, and ophthalmoplegia), lymphoma, malignancy (regional lymphadenopathy, splenomegaly), endocarditis (new or changing heart murmur), peripheral neuropathy (paresthesias with sensory, motor, and autonomic nerve dysfunction), and alcohol abuse (icterus, hepatomegaly).

**Table 38.1: Causes of night sweats**

Causes	Common examples
Infections	TB ( <i>Mycobacterium tuberculosis</i> ) Lung abscess Endocarditis HIV ( <i>Mycobacterium avium complex</i> ) Fungal (histomycosis, coccidiomycosis)
Malignancy	Hodgkin's and Non-Hodgkin's lymphoma Leukemia Solid tumors—Neoplasm (primary or metastatic)
Drugs/substance abuse	Antipyretics, insulin, antipsychotics, antihistamines, drug withdrawal in addicts—alcohol, heroin, opioids
Endocrine	Diabetes mellitus (nocturnal hypoglycemia) Hyperparathyroidism Endocrine tumors (pheochromocytoma, carcinoid tumor)
Others	Menopause Premature ovarian failure Pregnancy Anxiety/panic disorder Chronic fatigue syndrome Prinzmetal's angina Gastroesophageal reflux disease Obstructive sleep apnea Sleep terror Dumping syndrome Hypoglycemia of various causes Diabetes insipidus Takayasu's arteritis Temporal arteritis

## RED FLAGS

- Hyperhidrosis in hypoglycemia, acute coronary syndrome, and autonomic hyperreflexia (spinal cord injury); and hypohidrosis or anhidrosis in heat stroke indicate medical crisis.
- Hyperhidrosis beginning later in life should prompt a search for secondary causes such as systemic diseases, adverse drug reactions, or metabolic disorders.
- Older patients may not exhibit sweating because of a decreased sweating mechanism; hence they are at increased risk of developing heatstroke in high temperature.

## SELECTIVE GLOSSARY

**Frey syndrome**—It is a known complication after parotidectomy, and manifestations range from erythema related to eating to copious gustatory sweating. The cause is believed to be an aberrant connection of the parasympathetic fibers to the sweat gland of the overlying flap of skin.

**Harlequin syndrome**<sup>\*\*</sup>—A term originally reserved for patients with asymmetrical facial flushing and sweating without ocular signs of Horner's syndrome, is a rare autonomic condition characterized by flushing and sweating that occurs only on one side of the face and may occur for no apparent reason or in response to such things as heat and exercise. Since unilateral facial flushing can also be the first symptom of more serious conditions such as malignancy or stroke, a thorough diagnostic investigation is required to determine the underlying etiology of the condition. Occasionally, patients with Harlequin syndrome display symptoms that are also seen in Adie's syndrome (tonic pupils with hyporeflexia) or Ross syndrome (tonic pupils with hyporeflexia and segmental anhidrosis). The groups of symptoms seen in these syndromes, however, indicate a wider spread of autonomic deficits than those seen in pure Harlequin syndrome, with involvement of other parts of the nervous system. This point should be considered when making the differential diagnosis. The syndrome is usually of benign nature and does not require treatment unless neurovascular compression signs and symptoms are present.

<sup>\*\*</sup> The term Harlequin syndrome is also used to describe an autosomal recessive skin disorder that represents the most severe form of congenital ichthyosis.

**Nail Patella Syndrome (NPS)**—It is inherited as an autosomal dominant trait involving organs of both ectodermal and mesodermal origin. The diagnostic tetrad includes fingernail dysplasia, absent or hypoplastic patellae, the presence of posterior conical iliac horns, and deformation or luxation (i.e. hypoplasia) of the radial heads. Patients often complain of palmo-plantar hyperhidrosis. Kidney disease and glaucoma are now recognized as part of the syndrome. The most serious complication associated with NPS is nephropathy. The correct diagnosis is rarely established during childhood because the nail and patella abnormalities may not become apparent until later in life.

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## CHAPTER

# 39

## Swelling of the Legs

### SYNOPSIS

*Swelling of the legs* is commonly due to systemic edema state. *Edema* is the excessive accumulation of fluid in the tissues (or serious sacs\*) due to increase in the volume of interstitial fluid (ISF), i.e. increase in the extravascular portion of the extracellular compartment. In an adult, the ISF should expand by at least 2 liters<sup>†</sup> before the abnormality is clinically recognized as *pitting edema*, i.e. persistence of indentation of the skin following pressure.

In response to gravity, dependent edema first appears in the feet and ankles in an ambulatory patient, commonly called *pedal edema*<sup>‡</sup>. The patient usually complains of swollen legs, swelling of ankles towards evening around the top of the boot, weight gain, enlarged abdominal girth, and puffiness of the face, particularly in the morning.

Although a variety of clinical conditions, ranging from benign, e.g. dependent edema, to

potentially life-threatening condition, e.g. deep venous thrombosis is associated with pedal edema, diagnosis is simplified by determining localization of edema, i.e. whether one or both legs are involved, its onset—sudden or gradual, presence of pain, and other signs and symptoms of inflammation, and associated systemic symptoms such as breathlessness, jaundice, unexplained weight gain, sleep apnea, etc.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Cardiac (CHF—particularly right sided failure, cor pulmonale)
- Hepatic (cirrhosis of the liver)
- Renal (nephrotic syndrome, i.e. NS; acute glomerulonephritis; chronic renal failure)
- Venous disease (deep venous thrombosis, i.e. DVT; superficial venous insufficiency: varicosity, postsaphenous vein harvest)
- Drugs (calcium channel blockers)
- Endocrine (myxedema)
- Infection (cellulitis)
- Parasitic (lymphatic filariasis)
- Idiopathic edema (i.e. cyclical edema in women: *vide infra* ↓↓)

\* Pleura, peritoneum, pericardium, etc. referred to as 'third spaces'.

<sup>†</sup>At least 15% increase in body weight is necessary to demonstrate pitting edema.

<sup>‡</sup>*Presacral edema* appears in bed-bound patients.

- Premenstrual syndrome
- Pregnancy (normal, preeclampsia)
- Armchair legs (prolonged legs dependency).

#### Occasional

- Cardiac (chronic constrictive pericarditis, tricuspid valvular disease)
- Venous/lymphatic obstruction (i.e. secondary lymphedema, e.g. due to abdominal or pelvic mass, tumor, lymph node resection, irradiation)
- Lipedema
- Pretibial myxedema (Graves' disease)
- Rebound edema (sudden stoppage of diuretics/diuretic abuse)
- Chronic laxative abuse (hypokalemic edema)
- Malnutrition/malabsorption
- Hypercoagulability state (*vide infra* ↓↓: antiphospholipid syndrome, i.e. APS).<sup>1, 2</sup>

#### Rare

- Popliteal cyst rupture
- Gastrocnemius muscle rupture
- Retroperitoneal fibrosis
- Congenital (i.e. primary lymphedema, e.g. Milroy's disease).

### INVESTIGATIONS—GENERAL

#### CBC

- Iron deficiency anemia, megaloblastic anemia may be seen in nutritional deficiency diseases.
- Leukocytosis in cellulitis, thrombophlebitis, DVT.

#### Urinalysis

- Mild-to-moderate proteinuria (under 3.5 g/day).
- Hematuria, RBC casts in acute glomerulonephritis.
- Heavy proteinuria (> 3.5 g/day) is most often associated with NS.

- Microscopically—Urine sediment may show fat-body casts in NS.

#### Serum Protein (Total)

- Decreased in cirrhosis, NS, malnutrition, malabsorption, and neoplasms.

#### Lipid Profile<sup>3</sup>

- Hyperlipidemia in NS, which typically includes:
  - Increase in lipoprotein (a), LDL, VLDL, and/or IDL fractions.
  - No change or decrease in HDL.
  - Increase in LDL: HDL cholesterol ratio.
  - Increase in triglyceride levels.

#### LFT

- An elevated serum bilirubin level; abnormal transaminases, and alkaline phosphatase; and reduced albumin level are common with hepatocellular and cirrhosis of the liver.

#### TFTs

- Abnormal TSH values can point to either hypothyroidism or hyperthyroidism.

#### ECG

- For evidence of LVH, hypokalemia.

### INVESTIGATIONS—SPECIFIC

#### Duplex US (Compression US) with Doppler

- It is the preferred first line investigation for the evaluation of patients with superficial and deep venous thrombophlebitis and venous insufficiency. It is easy to perform, less expensive than most high-tech studies, can be performed as a portable examination, and with proper attention to technique, sensitivity of this test is approximately 97%.<sup>4, 5</sup>

**D-dimer Test**

- A positive plasma D-dimer test, in association with Duplex US of lower limbs and HRCT of lungs favor DVT and PE respectively.<sup>6</sup>

**Brain Natriuretic Peptide (BNP)**

- Helpful to rule out CHF in patients with dyspnea.

**Magnetic Resonance Venography<sup>§</sup> (MRV)**

- 3D-gadolinium-enhanced test may be recommended in patients in whom DVT of lower extremity (or occlusion of the large systemic veins, e.g. occlusion of the superior vena cava) is strongly suspected but US is equivocal. The positive diagnosis and extent of DVT can be easily detected and monitored by this noninvasive MRV technique.<sup>7, 8</sup>

**US/CT Abdomen/Pelvis**

- To detect secondary pressure effects from abdominal/pelvic mass, including ascites
- CT/MRI of the abdomen is preferred to diagnose retroperitoneal fibrosis (as a cause of venous thrombosis, or DVT).

**Echocardiogram**

- To evaluate for thromboembolic etiology in CHF and valvular heart disease
- An echocardiogram is recommended in patients who are at risk for pulmonary hypertension, and in patients over age 45 with leg edema of unclear etiology.

**Serology for Hypercoagulability State<sup>9</sup>**

- Plasma homocysteine level, lupus anti-coagulant, anticardiolipin antibodies, anti-beta 2 glycoprotein 1 antibodies, and a study of the

erythrocytic aggregation would appear to be of value in patients presenting recurrent with arterial or venous thromboembolic events.

**Biopsy**

- Renal biopsy in glomerulonephritis and NS.
- CT guided biopsy to confirm retroperitoneal fibrosis.

**CLINICAL NOTES**

- The initial clinical approach is to distinguish between unilateral and bilateral pedal edema (Table 39.1).

**Table 39.1: Causes and localization of swelling of the legs**

Unilateral	Bilateral
<ul style="list-style-type: none"> <li>• DVT</li> <li>• Chronic venous insufficiency</li> <li>• Cellulitis / abscess</li> <li>• Lymphedema—secondary causes</li> <li>• Arthritis</li> <li>• Trauma</li> <li>• Compartment syndrome (chronic)</li> <li>• Ruptured Baker cyst</li> <li>• Ruptured gastrocnemius muscle</li> <li>• Erythema nodosum</li> <li>• Kaposi's sarcoma</li> <li>• Neoplasm</li> <li>• Lymphedema—primary</li> <li>• Lymphedema praecox</li> <li>• Congenital venous malformation</li> </ul>	<ul style="list-style-type: none"> <li>• CHF</li> <li>• Cirrhosis of the liver</li> <li>• Nephrotic syndrome</li> <li>• Acute glomerulonephritis</li> <li>• Chronic renal failure</li> <li>• Hypoproteinemia</li> <li>• Bilateral DVT</li> <li>• Chronic venous insufficiency</li> <li>• Drugs</li> <li>• Lymphedema—secondary causes</li> <li>• Lipedema</li> <li>• Idiopathic edema (cyclical)</li> <li>• Pregnancy</li> <li>• Armchair legs</li> <li>• Constricting garments</li> </ul>

- Duration—Acute onset (usually <72 hours) is common with thrombophlebitis, DVT, cellulitis, ruptured popliteal cyst, etc. Gradual onset is common with systemic cardiac, hepatic, and renal disorders; chronic venous insufficiency, lymphatic and venous obstruction, etc. Intermittent edema is a common feature of idiopathic (cyclical) edema that is common in obese women.

<sup>§</sup> The standard investigation *contrast venography* is now replaced by Duplex US; the former is in most cases; they are expensive, invasive, and associated with a small but real incidence of phlebitis.



- Is the pedal edema pitting or non-pitting, i.e. solid? (Table 39.2).

**Table 39.2:** Common examples of pitting vs nonpitting edema

<i>Pitting edema</i>	<i>Nonpitting</i>
<ul style="list-style-type: none"> <li>• CHF</li> <li>• Cirrhosis of the liver</li> <li>• NS</li> <li>• Hypoproteinemia with severe anemia, e.g. protein-losing enteropathy, starvation, nutritional edema.</li> <li>• Pericardial effusion</li> <li>• Constrictive pericarditis</li> <li>• Drugs, e.g. calcium channel blockers</li> <li>• Venous obstruction/insufficiency</li> <li>• Beriberi (epidemic dropsy)</li> </ul>	<ul style="list-style-type: none"> <li>• Myxedema (deposition of mucinous material)</li> <li>• Parasitic, e.g. filariasis</li> <li>• Allergic, e.g. angio-neurotic edema</li> <li>• Postoperative, e.g. excision of malignant regional lymph nodes</li> <li>• Neoplastic, e.g. lymphatic blockage by malignant-tissue</li> <li>• Post-thrombotic syndrome</li> <li>• Idiopathic in women</li> <li>• Scleroderma</li> <li>• Congenital, e.g. Milroy's disease</li> </ul>

- Is it *lipedema* or *lymphedema*? Lipedema (a form of fat maldistribution with sparing of feet) exclusively affects women and is a bilateral and symmetrical deposition of fat in the lower extremities, *without* involving the feet; whereas in lymphedema the swelling starts in the most distal part of the foot (marked foot and toe involvement); this differentiates the two conditions.
- History of recent limb immobilization or confinement to bed following surgery, pregnancy, or history of cancer favors the diagnosis of DVT.
- Associated symptoms—Dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea suggests heart failure as the cause of leg edema. Jaundice, palmar erythema, spider angiomas, and hepatomegaly suggests cirrhosis of the liver. Generalized edema and swelling of the eyelids (peri-orbital) is typical with NS. If the leg swelling is absent or minimal after recumbency but develops as

the day progresses, then venous insufficiency is most likely.

- A common but under-recognized cause of leg edema is pulmonary hypertension, which is often associated with sleep apnea. Findings that may increase suspicion of sleep apnea include loud snoring or apnea noted by the sleep partner, daytime somnolence, or a neck circumference >17 inches.
- Is the patient taking any drugs that could cause the edema? Among the drugs that should be considered are corticosteroids; hormones—progesterone, estrogen, androgens; NSAIDs; antihypertensive drugs—calcium channel blockers, vasodilators, beta-adrenergic blockers; hypoglycemics—pioglitazone, rosiglitazone; antidepressants—trazodone, and chemotherapeutic agents.
- Morning and evening chart of patient's weight—Patients should weigh themselves nude and with an empty bladder before food or fluids in the morning and at bedtime. A mean weight gain >1 kg is consistent with idiopathic edema.<sup>10</sup>
- Physical examination—Lower limbs should be examined in the erect and recumbent positions for dilated superficial veins and perforators.
- *Homans' sign*, if positive (pain on dorsiflexion of the ankle), indicates DVT.
- Signs of systemic illness associated with swelling of the legs include—Periorbital edema, jaundice, spider angioma, peau d'orange skin, gynecomastia, ascites, hepatomegaly, cardiomegaly, distended neck veins, gallop rhythm, tachycardia, lung crepitations, hypertension, and lymphatic obstruction.

## RED FLAGS

- Patients with unexplained acute lower limb swelling should have duplex sonography

done since DVT is difficult to exclude on clinical grounds.

- Any painless unilateral leg swelling in women over age 40 years needs detail investigations to exclude intraabdominal lymphatic and venous obstruction, especially compressing gynecologic malignancy.
- Bilateral leg edema, in the absence of signs of CHF, and without lung disease, may be a useful marker for underlying pulmonary hypertension and obstructive sleep apnea, especially in obese patients.<sup>11, 12</sup>
- Pedal edema in patients with *unexplained thrombosis* is known to occur due to *combined thrombotic lesions* \*\* of peripheral veins as well as the arteries such as in hypercoagulability state, e.g. lupus, APS, occult malignancy, etc. It is of major importance to make this diagnosis so that patients can be treated with the most effective therapy for secondary prevention.

## SELECTIVE GLOSSARY

**Hypercoagulable states**—It can be defined as a group of inherited and/or acquired molecular defects that are associated with a predisposition to venous thrombotic events (including upper- and lower-extremity DVT with or without PE, cerebral vein thrombosis, and intraabdominal venous thromboses); arterial thrombosis (including myocardial infarction, stroke, acute limb ischemia, and splanchnic ischemia); or both. Although most *inherited* conditions appear to increase solely the risk of venous thromboembolic events, some of the *acquired* conditions have been associated with both venous and arterial thrombosis (Table 39.3). The best clue for the presence of hypercoagulability is

\*\* Venous thrombosis occurs mostly in the lower limbs, with or without pulmonary embolism, and cerebral ischemia and transient ischemic attacks, followed by coronary ischemia are the most common arterial events.

**Table 39.3:** Causes of hypercoagulability

### Acquired

- Antiphospholipid syndrome (APS)
- Hyperhomocysteinemia
- Inflammatory disorders: Ulcerative colitis
- Heparin-induced thrombocytopenia
- Myeloproliferative disorders
- Estrogens: Contraceptive pills, hormone replacement therapy

### Inherited

- Activated protein C resistance (factor V Leiden)
- Protein C deficiency
- Protein S deficiency
- Dysplasminogenemia
- Abnormal plasminogen
- Antithrombin deficiency
- Prothrombin 20210A allele
- Elevated factor VIII

### Risk Factors

- Disseminates intravascular coagulation
- Connective tissue disorders
- Malignancy
- Liver disease
- Pregnancy
- Bed rest
- Surgery
- Trauma

a positive family history. Clinical suspicions occur when patients are seen with unexpected venous thromboembolic disease, recurrent thrombosis, or thrombosis at unusual sites, such as the brain, portal vein, or hepatic vein. In addition, this entity should be considered in cases of unanticipated arterial occlusive disease of the central nervous system, extremities, mesenteric vessels, or cardiac tree.

**Antiphospholipid syndrome (APS)**<sup>13</sup>—It is probably the most common of the hypercoagulable disorders, which has received considerable attention from the medical community because of its association with a number of serious clinical disorders, including arterial and venous thromboembolism, acute ischemic encephalopathy, recurrent pregnancy

loss, thrombocytopenia, and livedo reticularis. It can occur within the context of several diseases, mainly autoimmune disorders, and is then called *secondary* APS. However, it may also be present without any recognizable disease, or so-called *primary* APS. The syndrome occurs most commonly in young to middle-aged adults; however, it also can occur in children and the elderly. This syndrome is the most common cause of acquired thrombophilia, associated with either venous or arterial thrombosis or both. It is characterized by the presence of antiphospholipid antibodies, recurrent arterial and venous thrombosis, and spontaneous abortion. Patients are often asymptomatic until suffering from thrombotic events of this syndrome such as DVT, pulmonary embolism, CVA, myocardial infarction, cardiac valvular dysfunction, and skin ulcers. In a rare patient with APS, a potentially devastating syndrome known as *catastrophic APS* (*Asherson's syndrome*) occurs, leading to massive venous thromboembolism, thrombotic microangiopathy, and multiple organ failure. According to the International Consensus statement, at least one clinical criterion (vascular thrombosis, pregnancy complications) and one laboratory criterion (lupus antioagulant, antipcardiolipin antibodies) should be present for the diagnosis of APS.

**Idiopathic edema**<sup>14</sup>—It includes entities such as cyclical edema, periodic edema, and fluid retention syndrome. It is an orthostatic edema accompanied by excessive weight gain from morning to evening that primarily affects premenopausal women, most common in their third and fourth decades. Although the cause is not clear, a number of hormonal abnormalities are postulated to be involved. These include rennin-angiotensin-aldosterone axis, vasopressin, atrial natriuretic factor, dopamine, hypothalamic disorders, and

thyroid disorders. In addition, exaggerated postural abnormalities, psychological or emotional disturbance, eating disorders, and abuse of diuretic or laxative are also associated with the onset of edema. It may also be associated with discomfort in the areas of fluid accumulation (including symptoms of the carpal tunnel syndrome, nonarticular rheumatism, and headaches, sometimes with pseudotumor cerebri). Key features are periodic episodes of edema in women who have weight changes not clearly related to the menstrual cycle. The diagnosis is usually one of exclusion.

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## CHAPTER

# 40

## Syncope

### SYNOPSIS

*Syncope*, commonly described as *fainting, passing out, or blackout*, is defined as a symptom complex that is composed of a sudden, and transient loss of consciousness, associated with an inability to maintain postural tone, followed by spontaneous and complete recovery, without medical intervention.\*

Syncope is distinct from vertigo, seizures, coma, and states of altered consciousness. Vertigo and dizziness do not result in loss of consciousness or postural tone. Vertigo is also associated with a sense of motion. Aura, violent muscular spasms, sphincter disturbances, disorientation, and gradual return to consciousness suggest a seizure.†

Evaluation of a patient with syncope is often problematic because episode usually occurs outside hospital, and accurate historical information (usually by an observer) is often lacking or conflicting. Moreover, patients are

often asymptomatic and no longer remember the event when seen by a physician.

Often the cause of syncope is benign and the condition is self-limiting; but, concerns that well-appearing patients may be at risk for potentially serious disorder‡ (e.g. acute coronary syndrome, malignant dysrhythmia, aortic dissection, and pulmonary embolism, as well as neurologic emergencies, such as subarachnoid hemorrhage) often leads to extensive diagnostic evaluation or hospital admission. However, many studies have demonstrated low yield of nondirected diagnostic testing.<sup>1, 2</sup> The pivotal role of the physician, therefore, is to identify those relatively few patients with life-threatening processes, and the majority with benign disorders needing *risk stratification*<sup>§</sup>, which will help devise an optimum evaluation and management plan for each patient.

\* i.e. - 'without any neurologic deficit and without using any electrical or chemical cardioversion'.

† Ref. Chapter 10: Convulsions, p. 63; and Chapter 47: Vertigo, p. 323 for details.

‡ It is said that, 'unless proved otherwise, syncope should be considered as an aborted second death'.

§ Risk factors for adverse outcomes include: age >45 years, structural heart disease, history of CAD, CHF, coexisting other systemic disease, ECG with non-sinus rhythm, family history of sudden death, and younger individual with exertional syncope.

## DIFFERENTIAL DIAGNOSIS

### Common

- Vasovagal (common *faint*)
- Situational syncope (cough, micturition, defecation)
- Postural hypotension (medications: Alpha blockers, nitrates, diuretics; diabetic autonomic neuropathy, pronged bed rest; varicose veins)
- Hypoglycemia (insulin, OHAs)
- Coronary artery disease (MI).

### Occasional

- Cardiac arrhythmia (heart block; Stokes-Adams-Morgagni syndrome: *vide infra* ↓↓; WPW syndrome: *vide infra* ↓↓; sick sinus syndrome: *vide infra* ↓↓; SVT; VT; Torsade de pointes: *vide infra* ↓↓; drug induced long QT syndrome, e.g. amiodarone, cisapride, erythromycin, gatifloxacin, thioridazine)
- Structural heart disease (aortic stenosis, HOCM, pulmonary stenosis)
- Cerebrovascular (TIA, stroke)
- Neurological (atypical absence/tonic seizures, basilar migraine: *vide infra* ↓↓)
- Circulatory failure (shock, hemorrhage).

### Rare

- Cardiac arrhythmia (Long QT syndrome: Congenital or drug induced)
- Psychogenic (anxiety, hyperventilation, hysterical)
- Pulmonary hypertension
- Pulmonary embolism
- Carotid sinus hypersensitivity
- Pacemaker syndrome
- Prosthetic heart valve dysfunction.

## INVESTIGATIONS—GENERAL

### ECG

- A 12-lead ECG should be ordered for all patients with syncope. A rhythm strip

during syncope (if faceable) is very helpful for any evidence of arrhythmia. (Table 40.1). A normal ECG in a patient with syncope may indicate good prognosis.

**Table 40.1:** ECG abnormalities in patients with Syncope

- Evidence of ischemia/infarction (recent or old)
- LVH (hypertension, aortic stenosis, HOCM)
- RVH (PE or pulmonary hypertension)
- Bradyarrhythmias or tachyarrhythmias
- LBBB or bifascicular block (conducting system disease)
- Signs of pericarditis or electrical alternans (cardiac tamponade)
- Classical/nonspecific ECG signs of PE
- WPW syndrome
- Long QT interval
- Brugada syndrome (partial RBBB with elevated ST segments in leads V1-3 and peculiar downsloping of the elevated ST segments + inverted T waves in those leads)
- Arrhythmogenic right ventricular dysplasia (RBBB, QRS complex > 110 msec in leads V 1-3, inverted T wave or epsilon wave.

### Blood Glucose

- *Functional* hypoglycemia may cause syncope in susceptible individuals under stress. Drug induced hypoglycemia is common in diabetics on insulin or oral hypoglycemic agents (OHA), which are often responsible for syncopal episodes.

### CBC

- Low Hb% (due to chronic blood loss, e.g. GI bleeding).

### Urea, Creatinine, Electrolytes

- To assess hydration status; hypokalemia, hyponatremia due to diuretic use; hypokalemia or hyperkalemia can precipitate arrhythmias.

## INVESTIGATIONS—SPECIFIC

### CXR

- Evaluation of a select number of etiologies of syncope may be aided by CXR. Pneumonia,



CHF, lung mass, effusion, and widened mediastinum can all be seen if present, and may guide therapy

- In elderly patients and in patients who are debilitated, pneumonia may precipitate syncope; pneumonia may occur in the absence of symptoms and signs in this class of patients.

### Cardiac Enzymes

- Indicated in patients in whom syncope due to cardiac origin is highly suspected, and those who give a history of chest pain with syncope, dyspnea with syncope, or exertional syncope.

### Stress ECG

- Indicated in patients with history of cardiac syncope, or cardiac risk factors are suggestive of IHD.

### Echocardiography

- Advised in syncopal patients who have an evidence of CHF, structural cardiac disorder (congenital or acquired), prosthetic valvular dysfunction, cardiomyopathy, cardiac tumors, pulmonary hypertension, or abnormal ECG findings. Evaluation of left ventricular function and ejection fraction is useful in the management of such patients.

### Holter Monitor

- Ambulatory Holter monitoring for 48 to 72 hours may be useful in patients with episodic syncope potentially associated with cardiac arrhythmias or silent ischemia.

### Carotid Doppler US

- Indicated if clinically there is evidence of carotid bruit or history suggestive of vertebrobasilar insufficiency (diplopia, hemiparesis).

### CT/MRI Brain

- Useful in patients with evidence of seizure, stroke disorder, new neurologic deficits, or in patients with head trauma secondary to syncope.

### Head-up Tilt-Testing

- Indicated especially in patients with recurrent or severe disorder of syncope as well as for high-risk patients (i.e. those at risk for injury if they faint). Hemodynamic response such as heart rate, blood pressure response, and ECG evidence for asystole associated with syncope are monitored. The test is used when cardiac causes of syncope have been reasonably excluded.

### Electrophysiology Study (EPS)

- An invasive procedure; may be indicated in patients with abnormal ECG revealing conduction abnormalities or arrhythmias; also in patients with recurrent unexplained syncope, with or without structural heart disease, and with negative results on tilt-table testing.

### Implantable Loop Recorder (ILR)

- These gadgets have up to two years worth of ECG recording capability and storage of cardiac rhythm. The device is programmed to store in memory cardiac rhythm after automatic or patient triggered activation, which provides high degree of 'symptom-ecg' correlation. This procedure is indicated only in patients with chronic unexplained syncope or in whom tilt-table test is negative.

### Electroencephalography (EEG)

- Indicated in selective patients in whom seizure is suspected or complicates syncopal attacks.

### Psychiatric Evaluation

- Indicated in patients with major depression, generalized anxiety disorder, panic, and substance abuse disorders.

### CLINICAL NOTES

- History is crucial to establish whether the patient did have an episode of *transient* loss of consciousness, and under what circumstances it occurred, e.g. prolonged standing, hearing bad news, physical exercise, micturition, etc
- An eyewitness to the event can help determine if seizure activity such as tonic-clonic muscle spasms, sphincter incontinence, or confusion after the spell was present. Presence of features such as aura, abrupt loss of consciousness, sensory hallucinations, *Déjà vu/jamais vu* experiences, confusional states, motor automatism, prolonged amnesia, and history of alcohol withdrawal, and head trauma favor seizure attacks
- Specific red flag symptoms such as chest pain, dyspnea, headache, and abdominal pain associated with syncopal event should raise concern about life-threatening causes, (Table 40.2); these should be excluded initially as they require immediate diagnostic evaluation, treatment, or hospital admission
- Other associated symptoms and clinical features (e.g. cardiac, neurologic, abdominal, or respiratory) may facilitate diagnosis of an underlying disorder such as acute coronary syndrome (ACS), seizure, GI hemorrhage, ectopic pregnancy, or pulmonary embolism (Table 40.3)
- Age—Noncardiac causes tend to be more common in young adults, while cardiac syncope becomes increasingly more frequent with advancing age. Syncopal episodes in elderly patients are difficult to evaluate due to multiple coexisting illness, medications, and physiological impairment as a result of aging. Advancing age heralds an increased frequency

**Table 40.2:** Red Flag symptoms in syncopal patients

Symptoms	Causes
• Chest pain, with or without palpitations or dyspnea; symptoms may be present as a presyncopal prodrome, following syncope, or both	• Myocardial ischemia or infarctions, aortic dissections, dysrhythmias, or pacemaker malfunction
• Dyspnea	• CHF, pulmonary embolism, tension pneumothorax
• Severe headache or new neurological deficits, with prodromal symptoms such as vertigo, dysarthria, diplopia, and ataxia	• TIA, stroke, subarachnoid hemorrhage, trauma
• Abdominal or back pain	• GI acute bleeding, e.g. ruptured abdominal aortic aneurysm; or in the pregnant patient, an ectopic pregnancy or placental abruption.
• Strenuous exertion just before syncope, especially in young athletes with a cardiac murmur	• Cardiac outflow obstruction due to aortic stenosis, HOCM, mitral stenosis, pulmonary stenosis, pulmonary embolus, left atrial myxoma, or pericardial tamponade.

- of CAD, arrhythmia, vasomotor instability, autonomic failure, polyneuropathy, and the use of polypharmacy—all of which can contribute to syncope. Besides, elder persons can present with atypical symptoms complicating syncope such as unexplained falls or lapses in memory. Therefore, advanced age is an independent risk factor for syncope
- Vasovagal syncope is the most common type of syncope, often initiated by a stressful, painful, or catastrophic experience. Premonitory symptoms such as nausea, sweating, pallor, palpitation, and a ‘sense of doom’ are usual
  - Situational syncope, e.g. on prolonged standing (postural syncope), while urinating (micturition syncope), on coughing (tussive syncope) are also common, especially in the elderly

**Table 40.3:** Clinical features suggestive of specific syncopal etiology

<i>Symptoms or findings</i>	<i>Tentative diagnosis</i>
Episode occurs on prolonged standing	Vasovagal syncope
Immediately on standing	Orthostatic hypotension (any cause)
After cough, micturition, defecation, swallowing, laughing	Situational syncope
Prodromal symptoms of nausea, sweating, lightheadedness, blurred vision, preceding pain, fever, unpleasant event	Vasovagal syncope
Lacerated tongue, jerking limbs, confusion, no memory of episode, sense of déjà or jamais vu	Seizure
Sudden, transient loss of consciousness without prodrome, underlying heart disease, palpitation	Arrhythmia
Syncope on exertion	CAD, HOCM, mitral stenosis, pulmonary hypertension
Syncope on head turning or pressure on the carotid sinus	Carotid sinus hypersensitivity
Associated with headaches	Migraine, seizure
Associated vertigo, dysarthria, diplopia	TIA
Dizziness/ syncope and murmur with changing position (from sitting to lying, bending, turning over in bed)	Atrial myxoma (left sided) or thrombus: <i>vide infra</i> ↓↓
Medication (QT-drugs)	Long QT syndrome
Frequent syncope, somatic symptoms, with negative clinical or lab work-up	Psychogenic disorder

- Orthostatic hypotension, i.e. decline in blood pressure greater than 20 mm Hg systolic, or diastolic greater than 10 mm Hg, or both, immediately upon rising from supine to standing position is a common cause of syncope, especially in the elderly, in diabetics, or those with autonomic neuropathy

- In patients with no known structural heart disease, a family history of unexplained cardiac death increases the likelihood of HOCM or congenital long QT syndrome
- Carotid sinus syncope typically occurs in relationship to head and neck movements, shaving, or wearing of tight collars around the neck (carotid sinus hypersensitivity)
- Effort (postexertional) syncope typically occurs in patients with aortic stenosis, hypertrophic cardiomyopathy, pulmonary hypertension, mitral stenosis, or CAD
- Cardiogenic syncope due to arrhythmia is often sudden in onset with loss of consciousness regardless of patient's posture; chest pain may also occur if the patient has IHD or aortic stenosis
- Syncope associated with brainstem dysfunction symptoms such as diplopia, ataxia, or vertigo are features of TIA involving vertebralbasilar system
- A comprehensive drug history is important in assessing whether medications have contributed to syncopal episode. Drugs commonly implicated in syncope include the following:
  - Antihypertensive drugs
  - Vasodilators—nitrates
  - Beta-blockers, digitalis, antiarrhythmics
  - Tricyclic antidepressants, phenothiazine, quinidine, amiodarone (long QT syndrome)
  - Alcohol, cocaine, sedatives
  - Diuretics (electrolyte imbalance)
  - OHA, insulin.
- Physical examination—Especially cardiac examination for heart rate, rhythm (arrhythmia); blood pressure (postural hypotension, hypertension); carotid bruit (TIA); presence of S<sub>4</sub> gallop, and crescendo-decrescendo murmur (aortic stenosis); late systolic murmur and nonejection click which changes in quality and radiation

(mitral valve prolapse); and pericardial rub (cardiac tamponade) are important

- The patient should have a detailed neurologic examination, including baseline mental status, evaluation for cranial nerve deficits, motor deficits, deep tendon reflex lateralization, and sensory deficits
- If the cause of the syncope is not readily apparent after initial clinical evaluation, then a decision has to be made whether certain categories of 'syncope-prone-patients' require admission to hospital. Examples of such subset of patients warranting hospitalization include:
  - Elderly patients >60 years with no apparent cause of the syncope
  - Sudden syncope occurring in a non-erect patient with no premonitory symptoms or prodrome
  - Sudden syncope occurring during exertion
  - Sudden syncope in a patient with a family history of syncope or sudden death
  - Patient has overt evidence of structural heart disease by history or examination
  - Patient has an abnormal ECG.

## RED FLAGS

- Occasionally, syncope may be confused with atonic seizure (i.e. 'drop attack', with sudden loss of postural muscle tone, consciousness briefly impaired, patient may collapse); EEG is indicated for differentiation
- Carotid sinus massage (to terminate tachycardias) should be attempted only under closely monitored conditions (with resuscitative equipment stand-by to manage the rare episode of asystole). It should not be attempted in patients if carotid bruit is present or with h/o recent stroke, TIA, or MI
- Patients with recurrent syncope of undetermined etiology (so called *malignant vasovagal syncope*<sup>3</sup>): who have no prodrome are at risk for injury to themselves or to others.

## SELECTIVE GLOSSARY

**Adams-Stokes attacks**—The term refers to a brief episode of cardiac arrest due to either asystole or ventricular fibrillation. This characteristically occurs in patients with heart block in whom either the ventricular pacemaker suddenly fails, or in whom ventricular arrhythmias are superimposed on the heart block. Prior to an attack, patient may become pale; heart rhythm experiences a temporary pause, and collapse may follow. Normal periods of unconsciousness last approximately thirty seconds; but if the attack is prolonged, convulsions may occur. The return of consciousness is accompanied by flushing as blood flows once more through vessels dilated by hypoxia.

**Atrial myxomas**—These are the most common primary heart tumors, originating from the fossa ovalis region of the atrial septum, usually occupying the left atrium. About 90% are solitary and occur sporadically. Approximately 10% are familial, transmitted in an autosomal dominant mode and can be part of several syndromes such as Carney syndrome (*vide infra* ↓↓). Multiple tumors occur in approximately 50% of familial cases and are more frequently located in the ventricle. Most myxomas are pedunculated with variable composition—from dense fibrous tissue with or without calcification to friable myxomatous tissue with propensity for peripheral embolization. The mobility of the tumor depends upon the extent of its attachment to the interatrial septum and the length of the stalk. Symptoms are produced by mechanical interference with cardiac function or embolization, and range from nonspecific and constitutional to sudden cardiac death. Clinical features include positional syncope, i. e. dizziness occurs as the patient changes position; dyspnea, pedal edema (CHF); TIA, stroke, seizures (cerebrovascular embolization); or features of collagen vascular disease. In about 20% of cases,

myxoma may be asymptomatic and discovered as an incidental finding. Signs and symptoms of mitral stenosis, endocarditis, mitral regurgitation, and collagen vascular disease can simulate those of atrial myxoma. A high index of suspicion aids in the diagnosis. Although transesophageal echocardiography is more sensitive, 2-dimensional echocardiography is usually adequate for diagnosis.

**Basilar Migraine (BM)**—Described by Bickerstaff in 1961, BM is a rare variant of migraine which frequently affects young women and girls, consists of headache accompanied by dizziness, ataxia, tinnitus, decreased hearing, nausea and vomiting, dysarthria, diplopia, loss of balance, bilateral paresthesias or paresis, altered consciousness, syncope, and sometimes loss of consciousness. Localized vertebrobasilar vasoconstriction leading to transient posterior circulation ischemia may contribute to the symptomatology of the disorder. Complications of basilar migraines include remote possibility of a basilar artery infarction.

**Carney Syndrome**—Carney first described an autosomal dominant multiple neoplasia syndrome featuring cardiac, endocrine, cutaneous, and neural tumors, as well as a variety of pigmented lesions of the skin and mucosae, which includes myxomas in breast, skin, thyroid gland, or neural tissue; potty pigmentation of skin and mucous membranes such as lentigines (i.e. flat brown discoloration of skin), pigmented nevi, or both; and endocrine overactivity such as Cushing syndrome. This syndrome belongs to a group of genetic disorders, the lentiginoses, which include Peutz-Jeghers, LEOPARD, and Laugier-Hunziker syndromes. The most serious manifestation of the Carney complex is cardiac myxomas.

**Sick Sinus Syndrome (SSS)**—It is also known as Sinus Node Dysfunction (SND), or tachy-

brady syndrome. It consists of a broad range of electro-physiological abnormalities, including inappropriate sinus bradycardia, sinus arrest, sinus node exit block, chronic atrial fibrillation, and bradycardia-tachycardia syndrome. The disease is commonly observed in older patients with a history of concomitant heart disease, but may also be observed in any age group, including adolescents and children. Its clinical manifestations vary widely. In the early stages of SSS, most patients are asymptomatic. As the disease advances, however, patients often seek medical attention for bradycardia-related symptoms. Syncope, near-syncope, and dizziness are the most frequently reported complaints, followed by palpitations, angina, or shortness of breath. Thromboembolic complications are a frequent cause of morbidity and mortality. Sudden cardiac death is possible at any point during the disease. Pacemaker placement is the cornerstone of treatment for symptomatic SSS.

**Torsade de Pointes**—A malignant form of polymorphic ventricular tachycardia that is characterized by heart rate between 200 and 250 beats per minute, and QRS complexes with changing amplitude and twisting of the points ('turning of the points'). The term also describes the syndrome of tachycardia with prolonged ventricular repolarization, long QT intervals exceeding 500 milliseconds or bradycardia. Torsades de pointes may be self-limited or may progress to ventricular fibrillation. The patient usually has syncopal attacks without premonition that lasts few seconds or seizures. It is commonly due to electrolyte imbalance or long QT drugs. There may also be history of congenital deafness or family history of sudden death.

**Wolff-Parkinson-White (WPW) syndrome**—WPW (preexcitation) syndrome is the most common accessory pathway SVT. WPW is mainly idiopathic or congenital, although it is



more common among patients with hypertrophic or other forms of cardiomyopathy, transposition of the great vessels, or Epstein's anomaly. In classic (or manifest) WPW syndrome, antegrade conduction occurs over both the accessory pathway and the normal conducting system during sinus rhythm. The accessory pathway, being faster, depolarizes some of the ventricle early, resulting in a short PR interval and a slurred upstroke to the QRS complex (delta wave). The delta wave prolongs QRS duration to  $>0.1$  sec, although the overall configuration, apart from the delta wave, may appear normal. Depending on the orientation of the delta wave, a pseudoinfarction pattern Q-wave may be present. Because the early depolarized parts of the ventricle also repolarize early, the T-wave vector may be abnormal. In concealed WPW syndrome, the accessory pathway does not

conduct in an antegrade direction; consequently, the above ECG abnormalities do not appear. However, it conducts in a retrograde direction and thus can participate in reentrant tachycardia. Symptoms of WPW syndrome may include palpitations, chest pain, dizziness, dyspnea, or rarely sudden death.

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## CHAPTER

# 41

## Tingling and Numbness

### SYNOPSIS

Abnormal cutaneous sensations such as tingling, numbness, pricking, shooting, cutting, stabbing, aching, burning, constricting, band-like, shock-like, etc. are caused by altered sensory nerve function. Such sensations which are perceived by an individual (i.e. subjective), *without* an apparent stimulus, excepting pain, are called *paresthesias*. *Dysesthesias* denotes all types of abnormal or unpleasant sensations, even painful ones, whether a stimulus is present or not.

While paresthesias and dysesthesias are subjective sensory phenomenon, other abnormal objective sensory abnormalities found on examination include hypoesthesia (decreased sensation to light touch, pressure, warm or cold stimuli), anesthesia (absent sensation to the same stimuli plus pinprick), hyperesthesias (exaggerated pain perception to touch), and allodynia (the perception of a nonpainful stimulus as painful, even excruciating).

This abnormal sensory dysfunction can result from six principal mechanisms, namely: Wallerian degeneration (e.g. from trauma or nerve infarction); axonal degeneration, sometimes referred to as *dying-back* phenomenon (e.g. metabolic diseases);

segmental demyelination (e.g. Guillain-Barré syndrome); compression (e.g. carpal tunnel syndrome); infarction (e.g. vasculitis); and infiltration (e.g. malignancy).

These mechanisms lead to various sensory symptoms and signs (as noted above) resulting from lesions at almost any level of the nervous system, including cortex (e.g. stroke syndromes), thalamus (e.g. Dejerine-Roussy syndrome), brainstem (e.g. lateral medullary syndrome, i.e. Wallenberg's syndrome), spinal cord (e.g. Brown-Séquard syndrome, syringomyelia), nerve roots (radiculopathies, plexopathies), and nerve trunks (neuropathies).

Peripheral nerve disorders are the most common causes of paresthesias and dysesthesias affecting a variety of peripheral nerve cells and fibers, including motor, sensory, and autonomic fibers. These are broadly referred to as peripheral neuropathies (PNs).

Most PNs affect both A and C types of nerve fibers to some extent. However, a single fiber type may be predominantly affected in some disorders; e.g. C-fibers, i.e. small-fiber neuropathy (SFN), in diabetes mellitus, and alcoholism. As small fibers subserve pain and autonomic functions, these neuropathies usually present with pain and

temperature loss, painful dysesthesias, autonomic dysfunction (anhidrosis, orthostatic hypotension, gastroparesis), or a combination. These patients will have normal motor function and deep tendon reflexes.

The large fibers, i.e. A fibers are myelinated motor fibers. These fibers are responsible for motion control, proprioception and vibration. The clinical presentation in patients with large-fiber neuropathy (LFN) are impaired vibration, gait instability, weakness, numbness, small muscle wasting, absent tendon jerks, but preservation of most cutaneous sensation. Dysesthesias, if present at all, tend to be tingling or segmental/band-like. Sensation for touch is carried by both small and large nerve fibers.

Although the diverse etiologies can make the diagnosis of PNs quite challenging, a systematic approach that classifies PNs on the basis of clinical features, taking into account the mode of onset (i.e. acute or chronic), type of peripheral nerve fiber that may be involved (i.e. sensory, motor, or autonomic), distribution (area of innervation of a nerve or central afferent system), associated neurologic symptoms and signs; and aided by specific laboratory evaluation and electrodiagnostic (EDx) tools will help in the final diagnosis of the disorder.

## DIFFERENTIAL DIAGNOSIS

### Common

- Diabetes mellitus - Type 1, 2; including IGT
- Alcoholism
- Upper extremity neuropathies (Tables 41.1 and 41.2)
- Lower extremity neuropathies (Tables 41.1 and 41.2)
- Acute stress disorders
- Hyperventilation
- Stroke syndromes

**Table 41.1:** Upper and lower extremity compression/entrapment neuropathies

<i>Upper extremity</i>	<i>Lower extremity</i>
<ul style="list-style-type: none"> <li>• Cervical radiculopathies (C5-C6orC7)</li> <li>• Brachial plexus neuritis (C5-T1)</li> <li>• Thoracic outlet syndrome (C5-T1)</li> <li>• Long thoracic nerve compression (winged scapula - C5,6)</li> <li>• Median nerve compression (carpal tunnel syndrome-C6-T1)</li> <li>• Ulnar nerve palsy (tardy ulnar palsy/claw hand-C8-T1))</li> <li>• Radial nerve palsy (wrist drop, Saturday night palsy, crutch palsy-C5-T1)</li> </ul>	<ul style="list-style-type: none"> <li>• Lumbosacral disc syndromes (disc herniation with nerve root compression (L4-L5 and L5-S1)</li> <li>• Sciatic nerve syndromes (L4-S3)</li> <li>• Femoral nerve neuropathy (L2-L3-L4)</li> <li>• Lateral femoral cutaneous nerve compression (meralgia paresthetica-L2-L3)</li> <li>• Posterior tibial nerve compression (tarsal tunnel syndrome-L5-S2)</li> <li>• Peroneal nerve compression (foot drop-L4-S1)</li> </ul>

- Renal failure
- Herpes zoster (postherpetic neuralgia)
- HIV/AIDS.

### Occasional

- Drugs (Table 41.3)
- Nutritional deficiencies (B<sub>1</sub>, B<sub>12</sub>, folic acid)
- Restless legs syndrome
- Guillain-Barré syndrome
- Cranial nerve neuropathies (Trigeminal neuralgia, facial palsy)
- Hypothyroidism
- Leprosy
- Syphilis (tabes dorsalis)
- Sarcoidosis
- Lyme disease
- Metabolic (hypokalemia, hypocalcemia, tetany).

### Rare

- Vasculitis syndromes (Wegener's granulomatosis)

**Table 41.2:** Common causes of peripheral neuropathies by distribution of involvement

<i>Distribution</i>	<i>Causes</i>
<b>A - Transient</b> upper/lower limbs	Normal, neurapraxia
<b>B - Upper limbs</b>	
• Bilateral	
– glove and stocking	Peripheral neuropathies
– along cervical nerve roots	Cervical radiculopathies Brachial nerve neuropathy Thoracic outlet syndrome
• Unilateral	
– peripheral nerve lesions	Carpal tunnel syndrome Leprosy Thoracic outlet syndrome Herpes zoster
<b>C - Lower limbs</b>	
• Bilateral	
– glove and stocking	Peripheral neuropathies
– more on exertion	Spinal (lumbar) canal stenosis
• Unilateral	Lumbosacral radiculopathies (infection, disc herniation, spondylosis, tumor) Meralgia paresthetica (lateral femoral cutaneous neuropathy) Herpes zoster

- Multiple myeloma
- Hodgkin's disease (non-Hodgkin's lymphoma)
- Paraneoplastic syndrome
- Malignancy
- Diphtheria
- Porphyria
- Toxins (organophosphorus compounds, lead, arsenic)
- Dejerine-Roussy syndrome (thalamic pain syndrome)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Hereditary (Charcot-Marie-Tooth syndrome).

**Table 41.3:** Drug induced polyneuropathies

Antibiotics
Chloramphenicol
Chloroquin
Dapsone
Ethambutol
Ethionamide
Isoniazid
Linezolid
Metronidazole
Nitrofurantoin
Lipid-lowering drugs
Statins
Antiretroviral drugs
Chemotherapeutics
Cisplatin
Cytarabine
Vinblastine
Vincristine
Cardiovascular
Ace-inhibitors
Amiodarone
Hydralazine
Rheumatologic
Allopurinol
Colchicine
Gold
Miscellaneous
Disulfiram
Interferon alfa
Lithium phenytoin
Pyridoxin
Statins
Thalidomide

## INVESTIGATIONS—GENERAL

### CBC

- For evidence of iron deficiency anemia, and macrocytic anemia.
- Leukocytosis in infection.

### ESR

- Elevated in systemic and inflammatory processes.

### Blood Glucose, Urea, Creatinine, Electrolytes

- As indicated for possible diabetes mellitus or renal disease.

**CXR**

- To rule out lung carcinoma and sarcoidosis.

**X-ray**

- In suspected trauma (e.g. Colles' fracture) or peripheral nerve compression as in hematoma, hypothyroidism, acromegaly.

**INVESTIGATIONS—SPECIFIC****TSH**

- In suspected hypothyroidism.

**Rheumatology Screen**

- RF factor, ANA to evaluate for connective tissue disease.

**Angiotensin-converting Enzyme Level**

- As indicated in sarcoidosis.

**Urine for Porphobilinogen**

- In cases suspected with porphyria.

**Nerve Conduction Study (NCS)**

- NCS predominantly attempts to distinguish the type of PN—axonal from demyelinating neuropathies. The former are characterized by decreased amplitude and to a lesser extent slowing on NCS; the latter show more marked slowing of the nerve conduction velocity. The most common type of axonal PN, a distal, symmetric, and predominantly sensory type, is called a *dying-back* neuropathy.

**CT/MRI**

- As indicated in stroke; cervical, thoracic, spinal compressive syndromes; thoracic outlet syndrome; multiple sclerosis.
- MRI of the brachial plexus may show evidence of infiltrating Pancoast lesion.

**Nerve Biopsy**

- Nerve biopsy, (sural nerve biopsy), may be used to assist in the diagnosis of some inflammatory, infectious, and metabolic PNs. Nerve biopsy may help to establish the

pathologic basis of the polyneuropathy when EDx studies cannot conclusively distinguish an axonal from an acquired segmental demyelinating disorder.

**Lyme Titer**

- In endemic areas with related Lyme disease manifestations.

**HIV**

- In patients with risk factors.

**Serum B<sub>12</sub> and Folate Levels**

- In suspected nutritional deficiency or if CBC shows macrocytic/dimorphic anemia.

**CSF Analysis**

- May be useful in the diagnosis of inflammatory (e.g. Guillain-Barré syndrome), infectious (e.g. Lyme disease, HIV), and a variety of immune-mediated PNs (e.g. vasculitic neuropathies).

**Serum Protein Electrophoresis and Immunofixation**

- For multiple myeloma or osteosclerotic myeloma (as seen in POEMS syndrome).

**Toxic Screen**

- Serum or urine drug / heavy metal screening if toxic neuropathy suspected.

**Genetic Test**

- For hereditary neuropathies or inherited metabolic disorders affecting nerves; Dejerine-Roussy syndrome, HMSN, type 1 (Charcot-Marie-Tooth disease), etc.

**CLINICAL NOTES**

- In normal persons tingling and numbness can occur transiently after sitting or sleeping

in awkward positions (sleeping with the arms above the head or sitting with the legs tightly crossed). This is due to sustained pressure on the nerve. These paresthesias causing temporary physiological paralysis but not degeneration, followed by complete and rapid recovery are called *neurapraxia*.

- There are three types of PNs:
  - *Mononeuropathy*—Characterized by a *focal abnormality* of a single nerve and usually results from local nerve trauma or compression;
  - *Mononeuropathy multiplex* (*multifocal neuropathy*)—Characterized by *asymmetric* abnormalities in more than one nerve trunk, which may occur simultaneously or over days to years; and
  - *PN*—Characterized by *symmetrical* abnormalities of sensation, motor strength, or both.
- Symptoms—Depend on the nerves affected; may involve sensory, motor, and/or autonomic systems.
  - *Sensory*—Tingling and numbness (paresthesia); burning sensation (dysesthesia); decreased sensation (hypoesthesia), loss of sensation (anesthesia), exaggerated pain perception (hyperesthesia), and *stoking-glove* pattern.
  - *Motor*—Mainly muscular weakness, muscle cramping and fasciculation causing difficulty with activities of daily living. Distal muscles are affected initially, e.g. weakness of dorsiflexion of the toes is common; diminished ankle reflex is often an early sign. Proximal muscles are involved later, except for inflammatory neuropathies such as PAN and SLE.
  - *Autonomic*—Abnormal (i.e. absent or excessive) sweating is an early symptom; postural hypotension, constipation, diarrhea, erectile dysfunction, and urinary retention occur only with advanced autonomic involvement.
- The most common causes of PNs are diabetes and alcoholism. In the absence of these two risk factors, obtain additional historical information, including history of trauma (compression/entrapment neuropathies), recent viral illness (Guillain-Barré syndrome), drug and toxin exposure (Table 41.2), occupation (exposure to industrial agents, pesticides), special diets (nutritional deficiencies), travel (Lyme disease), and risk factors for AIDS
- History of cancer, collagen vascular disease (vasculitis), hypothyroidism, and leprosy can be associated with PNs
- A detailed family history should include inquiries as to the presence of gait abnormality, muscular dystrophy, hammer toe, high arches, etc. to rule out inherited disorders such as Charcot-Marie-Tooth Disease (CMT)
- Onset—Generally gradual over months to years as in diabetes, alcoholism, renal failure, vasculitis, malignancy, etc. Causes of acute onset PNs include trauma, ischemic neuropathies, compartment syndromes, Guillain-Barré syndrome, porphyria, and Lyme disease
- Distribution (Tables 41.4 and 41.5)—Since sensory nerves innervate particular regions (dermatome)\* of the body, correlating the symptoms to areas of its supply is an important method to identify the nerves involved. For instance, the median nerve innervates the thumb, the first two fingers, half of the ring finger, and the part of the hand to which they connect, i.e. C6-C7 dermatome. The ulnar nerve innervates the other half of the ring finger, the little finger, and the remainder of the hand, i.e. C8 dermatome.

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\*Generally sensory loss does not occur in the entire corresponding dermatome; there is commonly a focus of paresthesias, dysesthesias, etc. within a wider area of impaired sensation in that dermatome.

**Table 41.4:** Neuropathies by pattern of involvement

Localization	Pattern	Most likely diagnoses
Mononeuropathy	Single nerve, e.g. ulnar nerve, median nerve, cranial nerve	Direct trauma, compression, entrapment (e.g. carpal tunnel syndrome, Tic douloureux)
Multiple mononeuropathy (mononeuropathy multiplex, multifocal neuropathy)	Simultaneous or sequential involvement of several nerves, evolving over days to years	Infections, granuloma, vasculitis, multiple entrapments (e.g. sarcoidosis)
Polyneuropathy	Longest nerves first (distal, stocking-glove pattern)	Metabolic, drugs, toxic, hereditary (e.g. diabetes mellitus)
Radiculopathy	One or more nerve roots	Herniated disk, spondylosis, herpes zoster
Polyradiculo-neuropathy	Proximal and distal weakness, sometimes asymmetrical	Guillain-Barré syndrome, CIDP, paraproteinemias
Plexopathy	Brachial	Trauma Idiopathic Neoplasm Radiation
	Lumbosacral	Diabetes Neoplasm Idiopathic Radiation

**Table 41.5:** Neuropathies by pattern of involvement

Focal	Multifocal
<ul style="list-style-type: none"> <li>• Trauma</li> <li>• Ischemic lesions               <ul style="list-style-type: none"> <li>– Diabetes mellitus</li> <li>– Polyarthritis nodosa</li> <li>– Reynolds's disease</li> </ul> </li> <li>• Entrapment neuropathies</li> <li>• Compressive neuropathies</li> <li>• Leprosy</li> <li>• Sarcoidosis</li> <li>• Neoplastic infiltration</li> </ul>	<ul style="list-style-type: none"> <li>• Diabetes mellitus</li> <li>• Nutritional deficiencies</li> <li>• HIV/AIDS</li> <li>• Leprosy</li> <li>• Sarcoidosis</li> <li>• Vasculitis               <ul style="list-style-type: none"> <li>– Polyarthritis nodosa</li> <li>– Systemic lupus erythematosus</li> </ul> </li> <li>• Multiple sclerosis</li> <li>• Chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP)</li> </ul>

- More diffuse involvement of an entire limb may be caused by involvement of the brachial (C5 to T1) or lumbosacral plexus (L1 to S3).
- Most often, PNs produce symptoms that are generalized and relatively symmetric, conforming to a distal-to-proximal gradient typical of *stocking and glove* distribution in the hands and feet, e.g. diabetes mellitus
- Unilateral involvement is seen in contralateral disease of the brainstem, thalamus, or cortex, e.g. stroke syndromes
- Multiple sclerosis may cause symptoms in several, widely separated areas
- Physical examination is performed to evaluate for possible systemic processes that may be contributing to the neuropathic process. Weight loss, fever, skin rash, icterus, lymphadenopathy, arthropathy, organomegaly are significant signs for possible systemic neurologic disorder
- Palpable thickened and/or tender peripheral nerves along with anesthetic skin patches are typical of leprosy
- Motor examination—Distal muscle groups are affected initially. Loss of muscle power progresses from distal to proximal. Deep tendon reflexes are diminished or absent
- Sensory examination—Which sensory tests (i.e. pain, touch, temperature, and vibration) to include in the physical examination depends on the clinical setting
- For patients with sensory complaints, testing for all the above four sensory modalities is necessary to uncover sensory *dissociation*, i.e. preservation of touch and vibration sensation, but loss of pain and temperature sensation, which is an important clue to incomplete spinal cord diseases such as in syringomyelia, spinal stroke (i.e. infarction of the anterior spinal artery), and Brown-Séquard syndrome.



- For screening diabetic feet and limbs, Semmes-Weinstein monofilament (5.07/10 gram) is recommended. The typical distribution of paresthesia is distal and symmetric, the feet being affected first in a stocking distribution followed by the hands in a glove distribution.
- The presence of *Tinel's sign* is useful to localize a nerve injury. The Tinel's sign refers to paresthesias elicited by tapping along the course of a nerve.
- Clinically LFNs can be distinguished from SFNs during sensory testing—Loss of vibration and proprioception indicates LFNs, while loss of pain and temperature sensation is due to SFNs. Loss of sensation for light touch may be due to LBNs or SFNs.
- Autonomic examination—Blood pressure measurement in supine and standing posture to check for signs of postural hypotension.
- Fundoscopy and examination of cranial nerves—It is important to detect optic pallor due to drug toxicity, hereditary demyelinating diseases, etc. Diabetes mellitus, leprosy, sarcoidosis, malignant lymphomas, myelomas, etc. are known to involve cranial nerves<sup>†</sup> (V, VII, IX, X, and XII) besides causing PNs.

## RED FLAGS

- Upper extremity paresthesias could be the sole manifestation of coronary syndrome, especially in individuals with cardiac risk factors.
- In older patients, PNs is not an uncommon presentation of many chronic illnesses, including neoplasms and inflammatory processes such as systemic lupus erythe-

matosis. Eliciting a full history, though often difficult in this population, is vital for accurate diagnosis and treatment.

- Leprosy must always be considered in a patient with a combination of skin and neural disorder.
- In the case of Guillain-Barré syndrome, the intensity of neuropathy may affect the muscles of respiration, necessitating the use of ventilatory support.
- Paresthesias and dysesthesias involving multiple cranial nerves palsies and radiculopathies, although similar in presentation to PNs, should alert one to the possibility of leptomeningeal metastasis; nerve biopsy is strongly indicated in etiologic diagnosis.
- An often dominating arm pain, which mainly radiates into the ulnar region, is a sign of the infiltration of the plexus and the C8 and T1 roots. The possibility of *Pancoast lesions*, typically caused by apical adenocarcinoma or squamous cell carcinoma of the lung should be considered not only in the presence of brachial plexopathy, but also when C8 or T1 radiculopathy is found, usually associated with ipsilateral Horner syndrome, characterized by miosis with a pupil that is slow to dilate, a mild (1-2mm) ptosis, ipsilateral anhydrosis and apparent enophthalmos.
- Although human rabies is rare cause of PNs, clinicians and public health workers should suspect rabies when a history of possible animal contact is known or when unexplained atypical progressive neuropathy or unusual febrile encephalitis is observed.<sup>1</sup>

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<sup>†</sup>With the exception of second cranial nerve.

## CHAPTER

# 42

## Tinnitus

### SYNOPSIS

*Tinnitus* is a common disorder with many possible causes. It is defined as any sound or noise in the ears or head not attributable to an external sound. It may be ringing, hissing, humming, and buzzing squealing, clicking, or popping noises.

Tinnitus may be unilateral or bilateral; transient or continuous. It may be acute—the episode usually lasting for seconds to minutes, but may persist for days to weeks; commonly due to noise trauma, or drug effect. Chronic tinnitus may persist for more than 6 months.

At the outset tinnitus should be differentiated from *auditory hallucinations* in which a person hears voices, various kinds of music or sounds, which are generally considered to be a symptom of psychiatric or neurological disorders.

Types of tinnitus—There are two categories:

1. Subjective:

- Audible only to the patient.
- More common form and may have its origin in the external ear, middle ear, inner ear, VIIIth nerve, or central nervous system.

- Common subtypes include: Otologic, neurologic, infectious, metabolic, drug-related, and psychogenic.

2. Objective:

- Also audible to the clinician (with the help of a stethoscope placed over head and neck structures near the patient's ear).
- Much less common than subjective tinnitus.
- Most common subtype is *pulsatile tinnitus*\*.
- May indicate treatable underlying medical condition.
- Frequently due to a vascular or neuromuscular condition: a tumor within the head, neck, or brain; or a structural defect in the ear, usually the inner ear.

The evaluation of a patient with tinnitus includes history, ENT-status examination, audiological and vestibular findings, imaging

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\* *Pulsatile tinnitus* is the type of ear noise that is perceived as a rhythmic pulsing that often synchronizes in time with the heartbeat. It can be experienced as a thumping sound. It is sometimes referred to as vascular tinnitus because in the majority of cases, it is related to disturbances in the blood flow.

investigations and, if necessary, examination by other specialists. Many medical and nonmedical treatments exist, with varying degrees of success and safety. Once the physician determines that the patient does not have a life-threatening or obviously treatable underlying condition, the patient should be counseled, reassured that the tinnitus is not a life-threatening disease, and offered appropriate treatment. All patients with tinnitus can benefit from patient education and preventive measures, and oftentimes the physician's reassurance and assistance with the psychologic aftereffects of tinnitus can be the therapy most valuable to the patient.<sup>1,2</sup>

## DIFFERENTIAL DIAGNOSIS

### Common

These may be considered under three groups, namely: Otologic, nonotologic, and psychogenic.

#### Otologic

- Cerumen impaction
- Foreign body
- Ear infection (acute otitis externa; otitis media: acute and chronic; labyrinthitis : viral, herpes zoster—geniculate ganglion)
- Otosclerosis
- Ménière's disease
- Positional vertigo (BPPV)
- Barotrauma/dysbarism.<sup>†</sup>

#### Nonotologic

- Migraine syndromes (migraine equivalent, acoustic migraine)
- Labile blood pressure (hypertension/hypotension)
- Diabetes (hypoglycemia)
- Thyrotoxicosis

<sup>†</sup>Injury following pressure changes; includes injury to the eustachian tube, ear drum, lung and stomach.

- Psychogenic (anxiety, depression)
- Ototoxic drugs (aspirin, NSAIDs, quinine, quinolones, loop diuretics, beta blockers, aminoglycosides, antipsychotics, anti-neoplastics, sedatives, narcotics).

### Physiological

- Presbycusis(sensorineural hearing loss with physiological aging).

### Occasional

- Noise induced permanent tinnitus<sup>3</sup> (i.e. NIPT: in factory workers, auto mechanics, airplane workers, rock musicians, military personnel with frequent exposure to gunfire, and those working around loud engines)
- Eustachian tube dysfunction
- Head and neck injuries (labyrinthine concussion)
- Neoplastic disorders (acoustic neuroma, glomus jugulare tumor: *vide infra* ↓↓).

### Rare

- Severe anemia, leukemia
- Temporomandibular joint (TMJ) dysfunction (subluxation, arthritis, ankylosis, synovitis)
- Atherosclerotic, vascular disorders (carotid artery aneurysm, arteriovenous malformation, vascular tumors)
- Neurologic (palatomyoclonus, idiopathic stapedial muscle spasm)
- CNS diseases (multiple sclerosis)
- Autoimmune inner ear disease (Cogan's disease: *vide infra* ↓↓).

## INVESTIGATIONS—GENERAL

### CBC, ESR

- Leukocytosis with infective ear disorders may be seen

- Severe anemia, including pernicious anemia, is rare causes of pulsatile tinnitus<sup>4</sup>
- Polycythemia vera, indicated by markedly elevated Hb% and hematocrit is known to cause transient neurological symptoms such as headache, tinnitus, dizziness, blurred vision, and paresthesias
- Elevated ESR is usually noted in autoimmune vestibulitis and neoplastic conditions.

### FBG, PPBG

- To detect diabetes.

### Audiogram

- A complete audiogram with pure tone and speech thresholds, speech discrimination, acoustic reflexes, and impedance testing is performed even if the patient is unaware of hearing loss.
- A formal audiogram establishes a base from which to pursue more advanced diagnostic testing.

### Tympanogram

- Tympanometry helps to identify previously undetected middle ear effusions, changes in tympanic membrane stiffness caused by a patulous eustachian tube, or myoclonus of the stapedial muscle or the muscles of the palate.

## INVESTIGATIONS—SPECIFIC

### Biochemistry

- Urea, creatinine, electrolytes, lipids, VDRL, FTA, ABS—if indicated by history and examination.

### TFTs

- If thyroid disorders suspected.

### CT Scan

- CT may be indicated for the assessment of patients with conductive hearing loss and

sensorineural hearing loss or vestibular disorders of the peripheral type. Most neoplasms and anomalies are best seen on bone algorithm CT studies.

### MRI Scan

- For patients with nonpulsatile tinnitus, MR imaging is the study of choice to exclude a vestibular schwannoma or other neoplasm of the cerebellopontine angle cistern. For asymmetric hearing loss or unilateral tinnitus, Gadolinium-enhanced MRI of the internal auditory canals is indicated to look for an acoustic tumor, and it is the procedure of choice for evaluating patients with suspected temporal bone tumors.

### MRI Cerebral Angiography

- Often indicated if vascular pathology—usually manifested as pulsatile tinnitus, e.g. arteriovenous malformations, vascular anomalies, and aneurysms of the carotid in the ear is suspected.

### X-ray

- Of the mastoids and petrous bones, and skull X-rays if associated with head injury.

### CSF

- Helpful in diagnosing multiple sclerosis and central nervous system syphilis.

### Brainstem Evoked Potentials

- In patients suspected with multiple sclerosis.

## CLINICAL NOTES

- Occasional tinnitus can occur in individuals with normal hearing, and most experience it in silent surroundings. Phantom noises, that mimic ringing in the ears associated

with tinnitus, can be experienced by people with normal hearing in quiet situations, according to a new research.<sup>5</sup>

- Evaluation of tinnitus includes, besides otoaudiological examination, an evaluation of psychosocial wellbeing of the patient, with special attention to signs of depression.<sup>6</sup>
- Is it subjective or objective? (see above)
- Objective tinnitus is unusual, but it may indicate glomus tumors, arteriovenous malformations, carotid stenosis, aneurysms, anemia, a patent eustachian tube, or myoclonus.
- If it is subjective, is it unilateral or bilateral? In general, pulsatile tinnitus, unilateral tinnitus, and tinnitus associated with other unilateral otologic symptoms represent potentially more serious underlying disease than bilateral tinnitus.<sup>7</sup>
- Episodic tinnitus suggests Ménière's disease. Pulsatile tinnitus suggests a vascular origin. Auscultation over the neck, periauricular area, orbits, and mastoid should be performed. Tinnitus of venous origin can be suppressed by compression of the ipsilateral jugular vein.
- Acute tinnitus, which can last days or weeks, may be caused by ear infection, medications, head or neck injury, excessive sound exposure, earwax, and changes in blood pressure or metabolism. With appropriate evaluation, such underlying conditions usually can be identified and treated, often with resultant resolution of tinnitus.
- Chronic tinnitus (persistence for 6 months or more) can also result from these conditions and is more likely to occur in people who have hearing loss.
- Concurrent medical conditions to be considered include diabetes, hypertension, thyroid disorders, hyperlipidemia, infection, anemia, B<sub>12</sub> or zinc deficiency.<sup>8</sup>
- Ototoxic drugs should be used with particular caution in patients who have risk factors that predispose them to ototoxicity,

such as advanced or very young age, renal or hepatic impairment, pregnancy, or history of hearing loss, or excessive and loud noise exposure.

- Ongoing audiologic monitoring for possible ototoxicity may be helpful when prolonged use of ototoxic agents is needed.
- Continued counseling about the risk of hearing loss is warranted if the patient is exposed to damaging sounds.
- Counselling, preferably including general information leaflet, is the cornerstone in the management of tinnitus in the vast majority of patients. There is no cure for tinnitus in the common sense of the word, especially in chronic cases. Many learn to live with their tinnitus when they are convinced of the non-threatening nature of their problem. Patients can obtain relief from the symptom with assistance from clinicians who are familiar with tinnitus management strategies.

### RED FLAGS

- Tinnitus plus unilateral hearing loss should increase suspicion for acoustic neuroma.
- The presence of other neurologic signs along with vertigo and deafness would suggest multiple sclerosis, advanced acoustic neuroma, basilar artery occlusion or insufficiency, brainstem tumors, and central nervous system syphilis.
- The severity of tinnitus varies from occasional awareness of a noise to an unbearable sound that drives some persons to contemplate suicide.<sup>9,10</sup>

### SELECTIVE GLOSSARY

**Cogan's syndrome**— It is a chronic inflammatory disorder that most commonly affects young adults. Clinical hallmarks are interstitial keratitis and vestibuloauditory dysfunction. Typical Cogan's syndrome consists of flares of interstitial keratitis and sudden onset of Ménière-

like attacks (nausea, vomiting, tinnitus, and vertigo and hearing loss). Life-threatening aortic insufficiency develops in 10% of reported cases. Atypical Cogan's syndrome (audiovestibular dysfunction with other types of inflammatory eye disease) is associated with vasculitis in 20% of cases, and has a less favorable prognosis than typical Cogan's syndrome.

**Glomus Jugulare Tumor**—A relatively rare, usually benign neoplasm—a paraganglioma arising from sympathetic or parasympathetic paraganglia outside the adrenal gland—originating in the chemoreceptor tissue of the carotid body, glomus jugulare, glomus tympanicum, and aortic bodies. Glomus tumors are encapsulated, slowly growing, highly vascular, and locally invasive tumors. Although most paragangliomas are sporadic, they can be familial. Glomus jugulare tumors occur predominantly in women in the fifth and sixth decades of life. The most common symptoms are conductive hearing loss and pulsatile tinnitus. Other aural signs and symptoms are ear fullness, otorrhea, hemorrhage, bruit, and the presence of a middle ear mass. Significant ear pain is uncommon. Involvement of the inner ear produces vertigo and sensorineural hearing loss. Cranial nerve involvement produces hoarseness and dysphagia. The presence of jugular foramen syndrome (paresis of cranial nerves IX-XI) is pathognomonic for this tumor, but it usually follows one year after the initial symptoms of hearing loss and pulsatile tinnitus. Less commonly, glomus tumors produce facial

nerve palsy, hypoglossal nerve palsy, or Horner syndrome. Because of the insidious onset of symptoms, these tumors often go unnoticed, and delay in diagnosis is frequent. Because of the location and extent of involvement, glomus jugulare tumors present a significant diagnostic and management challenge.

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## CHAPTER

# 43

## Tiredness

### SYNOPSIS

*Tiredness*\* is one of the most common and difficult presenting symptom to assess. Being a constitutional and nonspecific symptom, it may be less well-defined and explained by patients than symptoms associated with specific functions. Regardless of the cause, individuals may describe their sense of tiredness variously as exhaustion, weakness, loss of interest, low vitality, fatigue, or feeling *tired all the time* (TATT)—too tired to participate in family chore, work, or even leisure activities. It is often accompanied by a strong desire to rest or sleep.

Tiredness, being a nonspecific symptom, is multicausal, which can neither be quantified nor can be diagnosed with laboratory or imaging studies. Analyzing the symptom and reaching a diagnosis demands considerable skill, since tiredness may indicate the first subtle manifestation

of a serious and uncommon disease,<sup>1, 2</sup> or more commonly a normal occurrence as a result of full day's work, or sustained physical activity, or as a result of multiple potentially modifiable factors, which may be fully treated, or at least alleviated, thus increasing the well-being of the individual as well as potentially slowing the progression of disability.<sup>3</sup> In many cases no diagnosis can be made, leading the patient to repeat consultations, lab work, and multiple diagnoses.<sup>4</sup> Therefore, it is important for the physician to narrow down the vast differential diagnosis with an emphatic, structured approach, with an aim of cultivating a respectable and therapeutic relationship without extravagant investigations.<sup>5</sup>

### DIFFERENTIAL DIAGNOSIS

#### Common

- Physiological (overbusy lifestyle, sedentary lifestyle)
- Psychological (depression, anxiety, fibromyalgia: *vide infra* ↓↓)
- Acute postinfection syndromes (mostly postviral syndromes)
- Chronic infections (TB, hepatitis, HIV, AIDS)

\*Tiredness, fatigue, and weakness, though used interchangeably, convey different meanings. *Tiredness* is a state of subjective feeling of listlessness or lethargy which can occur at rest; whereas *fatigue* is an excessive tiredness on mental or bodily activity, lack of energy, which occurs in tasks requiring sustained effort. *Weakness* denotes a demonstrable reduction or loss of the strength or force of muscle contraction or power. *Exhaustion* is extreme fatigue, a marked loss of strength.

- Medications (diuretics, beta-blockers, antihistamines, tranquilizers, OTC agents)
- Substance abuse (alcohol)
- Systemic illness (anemia, hypothyroidism, diabetes mellitus, obesity, COPD, dehydration)
- Pregnancy (early stages)
- Menopausal syndrome.

### Occasional

- Major organ failure (cardiac, renal, liver)
- Sexual dysfunction<sup>†</sup>
- Sleep disorders<sup>‡</sup>
- Chronic fatigue syndrome (CFS).

### Rare

- Burnout syndrome (*vide infra* ↓↓)
- Hematological (leukemia, polycythemia)
- Malignancy (neoplasms)
- Lymphoma/granuloma
- Neurological (dementia, PD, MS)
- Endocrine (Addison's disease, thyrotoxicosis, hyperparathyroidism)
- Electrolyte/metabolic causes (hypercalcemia, sodium, potassium, periodic paralysis syndrome: *vide infra* ↓↓)
- Connective tissue disease (RA, PMR, SLE)
- Neuromuscular disorders (myasthenia gravis: *vide infra* ↓↓).

## INVESTIGATIONS—GENERAL

### CBC

- To assess the type and severity of anemia—generally IDA due to nutritional deficiency, chronic disease, or chronic blood loss.
- Leukocytosis in pyogenic infection.
- Marked leukocytosis with atypical WBCs in leukemia.

<sup>†</sup> Ref. Chapter 37 'Sexual dysfunction'. p 254

<sup>‡</sup> Ref. Chapter 28 'Insomnia'. p 189

### ESR

- Elevated in infection (TB, HIV); inflammation (RA, PAN); and malignancy.

### Blood Glucose

- Both hyperglycemia and hypoglycemia cause tired feeling.

### LFTs

- Markedly elevated liver enzymes when the liver is damaged by infections like hepatitis or by toxins like alcohol and certain drugs
- In a jaundiced patient an elevated bilirubin level is seen
- With chronic illnesses the albumin tends to gradually fall to low levels.

### Urea, Electrolytes and Creatinine

- An elevated serum urea or creatinine with dehydration or if the kidney function is impaired
- Hyponatremia and hypokalemia in patients on diuretic therapy
- Hyponatremia with hyperkalemia in Addison's disease
- Hypokalemia or hyperkalemia in periodic paralysis syndrome.

### TFTs

- Elevated THS with low FT4 in hypothyroidism.

### Pregnancy Test

- A urine or serum beta HCG level in all women of childbearing age may be indicated.

## INVESTIGATIONS—SPECIFIC

### CXR

- In patients with history of TB, tobacco CHF, smokers, and infection.

### Chronic Infection Screening

- TB, malaria, brucellosis, infective endocarditis, hepatitis serology (HBsAg, HCV antibodies), and viral markers (CMV, EBM).

**HIV and VDRL Serology**

- Should be considered in any patient whose history of sexual risk factors and examination is suggestive of the infection.

**RF and ANA**

- To screen for rheumatologic and autoimmune disorders.

**Plasma Cortisol (8 AM-10 AM Specimen)**

- Decreased serum cortisol (<3 mg/dl) generally, indicates Addison's disease.

**Muscle Enzymes CK, CK-MB**

- Increased levels in polymyositis, dermatomyositis, muscular dystrophy, drug-induced myopathy (e.g. corticosteroids, statins, gabapentin, colchicine, cyclosporin).

**Tensilon (Edrophonium) Test**

- The Tensilon test is best suited for examining focal weakness of ocular or pharyngeal muscles in suspected myasthenia gravis. If the lid ptosis is a result of myasthenia gravis, one will observe dramatic improvement in the ptosis within 30-45 seconds after IV Tensilon; lid ptosis typically will reappear 2-3 minutes later. The Tensilon test is positive in more than 90% of patients who have myasthenia gravis.

**EMG**

- In patients with neuromuscular transmission disorder (myasthenia gravis).

**Muscle / Tissue Biopsy**

- Distinguishes between neurogenic and myopathic disease
- Tissue biopsy to confirm malignancy.

**Bone Marrow Biopsy/Aspirate**

- In patients suspected with leukemia, lymphoma, lymphoproliferative disorders, and neoplastic disease.

**MRI Brain**

- If MS is suspected.

**Polysomnography (Sleep Study)**

- As indicated in patients with chronic insomnia.

**Cancer Screening**

- Age and gender-related cancer screening – for breast cancer, cervical cancer, endometrial cancer, colorectal cancer, lung cancer, and prostate cancer; or specific diagnostic methods may be indicated in patients with obscure cause of tiredness.

**CLINICAL NOTES**

- The primary purpose of evaluating a patient with tiredness is to identify its source or contributing factors. Exhaustive, unfocused evaluations are not likely to be rewarding
- It is very useful to ask patients to define their understanding of 'tiredness'. Characterizing the patient's complaints in terms of onset, associated symptoms, variability in symptoms, stressors, precipitating and alleviating factors, pre-existing medical conditions, and medications can help in narrowing the potential causes of tiredness and direct the initial investigations
- Similarly, family issues, including children, relatives, divorce, death, abuse, violence, trauma, financial difficulties, and habits should also be assessed
- Psychogenic—Tiredness existing for greater than 6 months, fluctuating in its severity, commonly

associated with family or social stressors, mood disturbances, and associated with either insomnia or early morning awakening (depression) is more likely to be psychogenic. The patient presents with multiple and non-specific symptoms with a normal physical examination.

- Organic—Tiredness from organic causes is acute in onset and shows a progressive course; stressors are often absent; family dynamics is sound and supportive. Sleep disturbances may be present, but is often related to the underlying disease process. Tiredness is less in the morning and worsens with activity. The patient presents with associated symptoms (Table 43.1), and the physical examination usually suggests potential underlying cause
- A *mixed* category of tiredness is more common which involves any of the above entries occurring in combination. One abnormality discovered may be treated and resolved without changing the patient's symptoms of tiredness (e.g. hypothyroidism or malignancy with depression). A balanced approach is essential to solve such problems
- In patients with tiredness, recognition of the symptoms of sleep deprivation is essential, as many such patients do not have a clear awareness of their own sleepiness. Therefore, a detailed '*sleep history*' (Ref. Table 28.1, page no.192) is mandatory, because sleep disorders are often associated with excessive daytime sleepiness which can be misunderstood by the individual as tired feeling<sup>6,7</sup>
- Physical examination— May reveal depressed patient with characteristic sad facial expression; skin pallor, petechiae, ecchymoses, purpura (anemia, leukemia); skin pigmentation (Addison's disease); lymphadenopathy (infection, leukemia, metastasis ); hepatosplenomegaly (infections, cirrhosis, malignancy, leukemia); stigmata of alcohol or drug abuse (gynecomastia, palmar erythema, needle tracks, infected skin lesions); and thyromegaly

**Table 43.1:** Tiredness: Historical symptoms and possible etiologies

Symptoms	Etiologies
Weight loss	Neoplasm; endocrine disorders (diabetes mellitus, hyperparathyroidism, thyrotoxicosis, Addison's disease); chronic infection (TB, infective endocarditis, HIV)
Weight gain	Obesity, hypothyroidism, Cushing's syndrome
Prolonged fever	Infective disease (TB, brucellosis, infectious mononucleosis, endocarditis, toxoplasmosis)
Alcohol, drug abuse, tobacco smoking	Cirrhosis of the liver, systemic toxic effect, COPD, lung malignancy
Polyuria	Diabetes mellitus, diabetes insipidus, hyperparathyroidism, chronic renal failure, hypercalcemia, Cushing's syndrome
Intermittent tiredness	Myasthenia gravis, familial periodic paralysis
Tiredness precipitated on carbohydrate meal, after exercise	Periodic paralysis syndrome
Female, tiredness after minimal exertion, hyperalgesic aches and pains, insomnia	Fibromyalgia
TATT, with no weight loss or abnormal work-up	Psychogenic disorder
Dyspnea, palpitation, increased sweating	Anemia (nutritional deficiency of iron, folic acid, malabsorption syndrome); CAD; cardiac valvular disease, COPD; thyrotoxicosis

(hypothyroidism, hyperthyroidism). Cardiac and lung examination may reveal the presence of  $S_3$  gallop, wheezing, or rales suggesting a cardiopulmonary etiology. A neurologic examination may identify neuromuscular disease as the cause (e.g. diplopia, ptosis,

dysphagia, dysarthria, limb weakness in myasthenia gravis).

### RED FLAGS

- A person may present his symptoms of tiredness as a *hidden agenda* or a *ticket of entry*: i.e. to discuss symptoms related to some personal beliefs, e.g. sexual dysfunction or HIV infection, and psychological symptoms. Such factors may be more important to the individual than fatigue or tiredness itself. Eliciting detail emphatic history usually uncovers these hidden agendas which reassures individual's help-seeking behavior.<sup>8</sup>
- Avoid exhaustive, unfocussed work up; they are not likely to be rewarding and in fact may be counterproductive, reinforcing the patient's belief in an existence of an insidious unidentified medical illness.
- Chronic tiredness, lasting over six months, for which diagnosis is elusive, should not be confused with CFS; however, the criteria for CFS may be considered for further evaluation.
- Chronic tiredness with depression or anxiety, suicidal ideation, and psychomotor retardation demands careful attention.<sup>9</sup>

### SELECTIVE GLOSSARY

**Burnout Syndrome**—It is a popular term rather than a scientific diagnosis denoting a severe state of exhaustion and cynicism that occurs frequently among individuals who do 'people-work' of some kind. Heavy workload, long hours, prolonged stress, poor coping mechanisms, low self-esteem are all associated with burnout syndrome. Some experts think the condition progresses through stages—alarm (stress arousal), resistance (energy conservation), and exhaustion. During the first stage, the person is irritable, forgetful, anxious, and unable to concentrate. Physical symptoms may include hypertension, palpitations, bruxism, insomnia, headaches, and GI problems. In the

energy conservation stage the person typically tries to compensate for stress with behaviors like procrastination, decreased sexual desire, social withdrawal, cynicism, apathy, resentment, and substance abuse. However, it's typically not until the final exhaustion stage that the person realizes that something is very wrong; symptoms include sadness, extreme fatigue, severe headache, and even suicidal ideation. Underlying depression or anxiety is common in such people—especially if there's suicidal ideation. A short-term psychotherapy or psychopharmacotherapy may be indicated for stabilization, although taking a simple break can cure some burnout.

**Fibromyalgia**—It is a poorly defined, complex, chronic, and disabling disorder that causes widespread pain and stiffness in the muscles, tendons, and ligaments with multiple tender points (*trigger points*); most frequent in women aged 20-50. Symptoms include generalized fatigue or tiredness, reduced physical endurance, pain in specific areas of the body, especially neck, shoulders, chest, back (upper and lower), hips and thighs, insomnia or poor sleep, sensations of numbness or swelling (although swelling is not actually present), chronic headaches, morning stiffness, worst on first arising, along with unrefreshing sleep and fatigue. It is commonly associated with conditions such as depression, anxiety, viral infection, CFS, eating disorders, physical or sexual abuse, IBS, tension headache, migraine, and hypothyroidism. Physical examination is normal except for *trigger points*; there are no specific tests for fibromyalgia; lab work up is normal.

**Myasthenia Gravis**—It is an autoimmune condition in which autoantibodies are developed against the acetylcholine receptors of neuromuscular junctions. The disease presents as fluctuating weakness and fatigability of voluntary muscles. The muscles of the eyes, head and neck are most commonly affected. Diplopia or unilateral ptosis is the initial symptoms in the majority. In severe cases, limb



and trunk muscles are involved and respiratory function may be compromised. Myasthenia gravis may be life-threatening when respiratory muscles are affected (myasthenic crisis). Initial symptoms may be subtle and only apparent at the end of the day or when the patient is fatigued. Exacerbations of myasthenia gravis may be precipitated by the use of anesthesia, narcotics or sedatives. Other autoimmune conditions, such as thyroid diseases and rheumatoid arthritis, are more common in myasthenia gravis patients and their families. The diagnosis is confirmed by the Tensilon test, electromyographic studies, and the finding of elevated acetylcholine receptor antibodies.

**Periodic Paralysis Syndrome**— (Familial Periodic Paralysis, Anderson-Tawil Syndrome)— It is a rare inherited autosomal dominant condition that causes occasional episodes of severe muscle weakness, commonly associated with thyroid disorders. Episodic bouts of severe weakness in the arms and legs are the most prominent symptoms. Typically these bouts occur during sleep, especially after strenuous activity. Cold, stress, and alcohol may also produce attacks. Other, less common, symptoms may include weakness in the eyelids and face muscles, muscle pain, arrhythmias, difficulty breathing or swallowing. The two most common types of periodic paralysis are *hypokalemic* and *hyperkalemic*. Some specific features to the type of periodic paralysis include:

- Hypokalemic:
  - Potassium levels are low during attacks.
  - Frequency of attacks varies from daily to yearly.
  - Attacks usually last between 4 to 24 hours, but can last for several days.
  - Attacks usually begin in adolescence, but they can occur before age 10.
- Hyperkalemic:
  - Potassium levels are high during attacks.
  - Attacks are usually shorter (lasting 1–2 hours), more frequent, and less severe than the hypokalemic form; breathing

and swallowing difficulties are extremely rare.

- Between attacks, patients often experience muscle spasms or difficulty relaxing their muscles, a condition known as myotonia.
- Attacks usually begin in early childhood

Giving oral glucose or glucose and subcutaneous insulin may trigger a hypokalemic attack, whereas giving potassium may trigger a hyperkalemic attack. Because this primarily is an inherited condition, the most important aspect of diagnosis is obtaining a family history.

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## CHAPTER

# 44

## Urinary Frequency

### SYNOPSIS

In an adult, *urinary frequency*, i.e. the number of voids per day varies considerably, depending on factors such as age, gender, weather, intake of fluids, food habits, voiding habits, cultural, and social influences.

At the physiologic level, urination (also known as micturition, voiding) is a reflex mechanism (spinobulbospinal reflex), facilitated and inhibited by higher brain centers (pontine micturition center), and subject to voluntary facilitation and inhibition. The normal bladder capacity in an adult is approximately 500 ml, but it can be voluntarily overridden until the content reaches 600-800 ml, when the conscious urge to void becomes difficult to ignore. However, the micturition reflex can yet be voluntarily inhibited until it is appropriate to begin voiding (e.g. a toilet is reached). Any condition which interferes with such compliance of the bladder wall, diminished bladder capacity, and increased irritability of the bladder or urethra will lead to repeated

desire to micturate. Similarly, increase urine output, i.e. polyuria, will result in increased frequency of micturition.

Normally in an adult with an average fluid intake, the act of micturition is initiated (as a reflex) when the urine volume is about 300-400 ml, and occurs 4 to 8 times during the day, and none or once during the night. Urinary frequency, strictly speaking, occurs when there is increased need to urinate more often without a concomitant increase in the volume of urine. With no accepted reference range;<sup>1-3</sup> urinary frequency may be arbitrarily defined as frequent urge to urinate without being able to pass much urine; patients may complain that they are voiding more often than they used to, but the total volume not exceeding 3L per day. If the total volume is >3L, it is termed *polyuria*.<sup>\*</sup> Two or more night time voids is termed *nocturia*, and *urinary urgency* is sudden compelling urge to urinate (patient has to hurry to the toilet), often accompanied by bladder pain.

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<sup>\*</sup> Ref. Chapter 34 Polyuria p. 234

It is critical to differentiate urinary frequency from *urinary incontinence*<sup>†</sup>, i.e. involuntary release of urine or loss of bladder control. The four common types of urinary incontinence include: *Stress incontinence*— Characterized by urine leakage associated with increased abdominal pressure from laughing, sneezing, coughing, climbing stairs, or other physical exertion.

*Urge incontinence*—A sudden, intense urge to urinate, followed by an involuntary loss (i.e. leaking) of urine. In urge incontinence, the bladder is said to be *overactive*; it's contracting even when it isn't full. Urge incontinence usually entails urgency, frequency, or nocturia. These symptoms are often referred to as the *OverActive Bladder syndrome* (OAB).

*Overflow incontinence*—It is incomplete bladder emptying, associated with frequent or constant dribbling of urine, secondary to impaired detrusor contractility or bladder outlet obstruction.

*Mixed incontinence*—It is the coexistence of stress and urge incontinence, characterized by involuntary loss of urine associated with urgency as well as exertion, cough, sneeze, or any effort that increase intraabdominal pressure.

These urinary symptoms, i.e. frequency, urgency, incontinence, and nocturia are commonly seen overlapping in patients with urologic and systemic disorders.<sup>4, 5</sup> The prevalence increases with age, and is more common in women. In the elderly, it is very common in both sexes. However, decisions concerning management depend on the cause of the frequency and the degree of bother that it causes the patient.

<sup>†</sup> According to the International Continence Society, urinary incontinence is defined as a condition of involuntary urine loss that is objectively demonstrable and is a social or hygienic problem.

## DIFFERENTIAL DIAGNOSIS

### Common

- Urinary tract infections (UTIs—cystitis, vaginitis, urethritis, pyelonephritis, prostatitis)
- Urethral syndrome<sup>‡</sup>
- Benign prostatic hypertrophy (BPH)
- Calculus (ureteric, bladder)
- Diabetes mellitus (Type 1 and 2)
- Diuretics
- Pelvic inflammatory disease (PID)
- Urinary incontinence
- Anxiety neurosis
- Pregnancy
- Cold weather.

### Occasional

- Interstitial cystitis
- Overactive bladder (irritable bladder)
- Renal tuberculosis (tubercular cystitis)
- Urethral strictures
- Pelvic space-occupying lesion (fibroid, ovarian cyst, carcinoma)
- Reiter's syndrome (i.e. urethritis, arthritis, and conjunctivitis).

### Rare

- Diabetes insipidus—cranial and nephrogenic
- Malignancy (bladder, prostate, rectum)
- Neurogenic—spastic bladder (e.g. sacral spinal cord lesion, trauma)
- Parkinson's disease
- Multiple sclerosis
- Urinary tract foreign body
- Postradiotherapy fibrosis.

<sup>‡</sup> Symptoms suggestive of cystitis and urethritis, usually in post-menopausal women with atrophic vaginitis, and post-coital sexual trauma.

## INVESTIGATIONS—GENERAL

### Urinalysis

- Microscopy<sup>§</sup>—leukocytes (10 or more WBCs /cu. mm in fresh\*\* unspun mid-stream urine sample), possible hematuria, granular casts, and red-cell casts are generally seen in UTIs.

### Quantitative Culture for Bacteriuria

- A conventional threshold count of  $>100,000$  (i.e.  $>10^5$ ) bacteria/ml indicates active infection
- In symptomatic patients a count of 100 to 10,000 (i.e.  $10^2$  to  $10^4$ ) bacteria /ml is recognized as an infection
- Count of  $<10,000$  (i.e.  $10^4$ ) bacteria /ml in the absence of therapy largely rules out bacteriuria<sup>††</sup> but pathogenic organisms may be present
- Count of 10,000 to 100,000/ml should be repeated and cultured.

### Suprapubic Aspiration/ Catheterization

- The presence of bacteriuria of any degree (i.e. any growth of pathogenic organisms) in suprapubic aspirates or of  $\geq 10^2$  bacteria /ml of urine obtained by catheterization is virtually diagnostic of UTI.

### CBC

- Leukocytosis in acute UTIs
- Peripheral blood eosinophilia may be an initial manifestation of eosinophilic cystitis.<sup>6</sup> (*vide infra* ↓↓).

### Blood Glucose

- Diagnosis of diabetes mellitus.

<sup>§</sup> Urine 'dipstick' test—both false-positive and false-negative results are common.

<sup>\*\*</sup> Early morning urine (EMU) sample preferred.

<sup>††</sup> Bacteriuria denotes the presence of bacteria in the urine, which may be symptomatic or asymptomatic.

### Urea, Creatinine

- Elevated with decreased renal function from chronic obstruction.

### Electrolytes

- Especially diuretic induced hypokalemia is important as it is responsible for the excess mortality observed in patients with diuretic treated essential hypertension and cardiac abnormalities.

### Pregnancy Test

- In all women of childbearing age with missed periods.

## INVESTIGATIONS—SPECIFIC

### Urine Culture

- Midstream clean-catch urine culture is indicated only in relapse, reinfection, and conventional therapy resistant UTIs, and in those with predisposing conditions such as complicated UTIs<sup>‡‡</sup>, diabetes mellitus, or immunocompromised state.

### US of Kidneys, Ureter, and Bladder (KUB)

- To detect renal size, calculus, obstruction, mass lesion, and to measure postvoid urine volume in BPH
- US of pelvis for prostate hypertrophy<sup>§§</sup> in men, and lesions of uterus, ovaries in women.

### CT Scan of KUB

- Contrast-enhanced CT for diagnosis and follow-up of complicated UTIs
- Dual-phase helical CT of kidney allows different phases of excretion to be studied

<sup>‡‡</sup> Complicated UTI indicates a UTI that occurs in a patient with a structural or functional abnormality of the genitourinary tract.

<sup>§§</sup> Transrectal US is preferred.

(nephrographic phase compared to corticomedullary phase) and can define the extent of the disease and identify significant complications and obstruction

- Renal masses, bladder, and prostate tumors and calculi, including lucent, low-density calculi (e.g. uric acid stones) are well seen on helical CT scan
- Limiting nonenhanced spiral CT (NECT) is the preferred choice in patients who do not have classical symptoms of renal colic; older patients, and in those with a contraindication to the administration of intravenous contrast media.<sup>7</sup>

### **Intravenous pyelography (IVP) or Intravenous Urography (IVU)<sup>\*\*\*</sup>**

- Largely replaced by US and CT scanning,<sup>8</sup> but still plays a role in the diagnosis of calculus disease.

### **MRI Brain/Spine**

- Indicated if cranial diabetes insipidus, e.g. polyuria due to pituitary craniopharyngioma is suspected
- To rule out spinal cord lesion from trauma, tumors, or spina bifida.

### **Cystoscopy**

- Indicated for patients with persistent irritative voiding symptoms—frequency, urgency, dysuria, or hematuria
- To diagnose bladder lesions such as cystitis, stone, tumor, and urethral strictures.

## **CLINICAL NOTES**

- Ask the patient how many times a day he or she voids, and how this compares to previous pattern of voiding

<sup>\*\*\*</sup> Magnetic resonance urography is preferred over IVU.

- Toileting record—One of the most helpful components of the history is the record kept by the patient or caregiver during a 48- to 72-h period. The chart records the volume and time of each void or incontinent episode. A detail list of questionnaire and 24 hr bladder diary is an extremely valuable tool to differentiate various voiding symptoms<sup>9</sup>
- Clarify whether frequent urination is associated with excessive urination, or frequent attempts to urinate with only reduced urine output; the former indicates frequency with polyuria, e.g. in diabetes mellitus, and the latter frequency alone, e.g. in UTIs, BPH
- An approximate estimate of how much fluids the patient is consuming in a day helps to determine hydration status, detect excessive thirst in diabetes mellitus and diabetes insipidus, and also detect habitual overdrinking
- Caffeine intake, alcohol abuse, and diuretics cause frequent urination. Some medications cause nephrogenic diabetes insipidus, e.g. lithium, leading to frequency and excess voiding
- Sexual history helps in assessing risk of sexually acquired urethritis
- Past history of CNS infection such as meningitis or hypothalamic-pituitary surgery is the common cause of diabetes insipidus resulting in polyuria and frequency
- Associated symptoms like fever, chills, loin pain radiating to groin, dysuria, urgency, terminal dribbling of urine, acute retention of urine, etc. are pointers to UTIs, calculi, and BPH
- Morbid anxiety is a common cause of urinary frequency; usually associated with other genitourinary and sexual symptoms such as dysuria, impotence, and frigidity. Other symptoms of anxiety such as palpitation, sweating, hyperventilation, dizziness, and headache are also present
- Physical examination includes assessing state of hydration, vital signs, abdominal palpation

for distended bladder due to retention or urethral obstruction. In women, pelvic examination, and in men digital rectal examination should be performed. Abnormal neurological findings such as deep tendon hyperreflexia or absence of the bulbocavernosus reflex suggest the possibility of underlying neurologic lesion.

### RED FLAGS

- UTI in male—In every male who has even one episode of UTI, a careful search must be made for possible cause; history of sexual exposure may need direct inquiry
- In all women of childbearing age, exclude pregnancy by doing a pregnancy test if a period has been missed. The chances of an unrecognized pregnancy presenting with polyuria can thus be minimized
- Urinary tract TB is a common masquerade; presenting in various systemic and genitourinary symptoms. Diagnosis depends on constant awareness, especially in patients with sterile pyuria
- In patients with irritative voiding symptoms associated with neurologic signs such as diplopia, blurred vision, paresthesia, consider neurogenic bladder—multiple sclerosis is a strong possibility
- Not all prostate hyperplasia is benign; periodic prostate cancer screening is indicated in select cases. Prostate cancer often is asymptomatic despite extensive spread
- Interpret elevated prostate specific antigen (PSA) with caution, as it may be elevated in both BPH and prostate cancer.

### SELECTIVE GLOSSARY

**Eosinophilic Cystitis(EC)**—It is a 'rare clinicopathological condition characterized by transmural inflammation of the bladder

predominantly with eosinophils, associated with fibrosis with or without muscle necrosis. The cause of EC remains unclear, although it has been associated with various etiological factors, such as allergy, bladder tumor, bladder trauma, parasitic infections and chemotherapeutic agents. EC is, probably, caused by the antigen-antibody reaction. This leads to the production of various immunoglobulins, which, in turn, cause the activation of eosinophils and initiates the inflammatory process. The most common symptom complex consists of frequency, hematuria, dysuria and suprapubic pain. Cystoscopy and biopsy are the gold standard for diagnosis. Additional laboratory evidence supporting the diagnosis includes proteinuria, microscopic hematuria and peripheral eosinophilia, the last one occurring in few patients. There is no curative treatment for this condition. Current treatment modalities include transurethral resection of the bladder lesion along with nonspecific medical therapy, such as nonsteroidal antiinflammatory agents or steroids. Because the lesion tends to recur in spite of the above therapy, long-term follow-up is mandatory'.<sup>10, 11</sup>

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## CHAPTER

# 45

## Urticaria and Angioedema

### SYNOPSIS

*Urticaria*\* is a heterogeneous group of disorders characterized by production of 'wheals', (also called as 'hives'), i.e. itchy, transient, erythematous, or pale, edematous swellings of the superficial layers of the dermis which blanch on pressure; each individual lesion is short-lived, lasts for few minutes to several hours, seldom more than 24 hours; episodes may recur daily or several times each day for days, or years. Wheals are rounded, oval, or ill-defined closely placed lesions which may coalesce to form various shapes and sizes from a few millimeters to few centimeters. Any part of the body may be affected, trunk being more commonly involved than extremities or face.

Angioedema is a condition which involves subcutaneous or submucosal tissue (rather than the dermis), with sudden, diffuse, nontender swelling of the involved parts, primarily of the

lips, periorbital areas, or genitalia. Occasionally there may be swelling of the tongue or pharynx which can be life-threatening, but the larynx is virtually never involved.<sup>1</sup> The pruritus that usually accompanies urticaria is conspicuously absent in angioedema.

Urticaria and angioedema may coexist. Angioedema accompanies urticaria in approximately 40% of patients, another 40% of patients have hives alone, and about 20% of patients have angioedema but not urticaria.<sup>1</sup>

Based on its duration, urticaria is classified into:

*Acute*—If the symptoms last less than 6 weeks; etiological trigger is more likely to be identified in acute urticaria such as drug reactions, and food or contact allergies.

*Recurrent acute urticaria*—This is recurrent episodes of urticaria, each episode lasting less than six weeks.

*Chronic*—If there are recurrent episodes occurring daily or almost daily for longer than six weeks. The history itself can be regarded as the most valuable diagnostic tool in identifying causes of chronic urticaria; extensive laboratory studies

\* Urticaria was described in 1772 by Heberden W. as "little elevations upon the skin in the 'nettle' rash that often appears involuntarily and seldom stays many hours in the same place. There is nobody exempt from 'them' and by far the greatest number experience any other evil from it besides the intolerable anguish arising from the itching..." (Heberden W. Of the Nettle Rash Transactions: College of Physicians, London, 1772; 2; 173).

provide little information beyond that suggested by the patient's history and physical examination.

From the patient perspective, chronic urticaria affects as many dimensions of the health-related quality-of-life as some life-threatening diseases or well-recognized disabling chronic skin disorders, such as psoriasis or atopic dermatitis. Recent trials have highlighted the serious disability of patients with chronic urticaria, including loss of sleep and energy, social isolation, altered emotional reactions, and difficulties in aspects of daily living. The disability is of the same order as that experienced by patients with severe chronic ischemic heart disease.<sup>2,3</sup>

## DIFFERENTIAL DIAGNOSIS

**Common** (the *In's* of hypersensitivity urticaria).

- Infections (occult bacterial infection involving sinuses, teeth, gums, gallbladder, chest, genitourinary tract; mycoplasma, *H. pylori* enteritis; viral infections: hepatitis A, B, and C, infectious mononucleosis; fungal infections: dermatophytosis, candidiasis)
- Infestations (protozoal and helminthic: Strongyloidiasis, giardiasis, amoebiasis, malaria)
- Ingestions (foods and food additives: eggs, sea-food, nuts, metabisulfites, tartrazine, azo dyes)
- Injections, i.e. drugs<sup>†</sup> (aspirin, penicillin, sulfonamides, opiates, ACE-inhibitors, blood products, herbal products)
- Inhalants (pollens, mold spores, animal danders, house dust, aerosols)
- Insect stings or bites (mosquitoes, flies, ants, bees, spiders)
- Contact urticaria (latex sensitivity, hair bleaches, *kumkum*, cosmetics, lipsticks, sunscreens, dental prosthesis, dental filling).

<sup>†</sup> Drugs taken as long as a month prior to the onset of symptoms may induce urticaria.

## Occasional

- Physical urticaria (dermographism; cholinergic urticaria; cold urticaria; solar urticaria)
- Pregnancy (Pruritic urticarial papules and plaques of pregnancy, i.e. PUPPP)<sup>4</sup>

## Rare

- Systemic disease (connective tissue diseases): Juvenile RA, SLE, vasculitis: *vide infra* ↓↓; endocrine disorders: Hashimoto's thyroiditis, Graves' disease, diabetes mellitus; neoplasms: lymphoma, leukemia, carcinoma, myeloma, Sweet's syndrome: *vide infra* ↓↓
- Skin diseases: Urticaria pigmentosa, i.e. mastocytosis; dermatitis herpetiformis; pemphigoid; amyloidosis
- Psychogenic urticaria: Depression, anxiety, stress
- Genetic: Autosomal dominant hereditary angioedema, i.e. HAE: *vide infra* ↓↓.

## INVESTIGATIONS—GENERAL

### CBC

- WBC count may be elevated in systemic or dermal infection; eosinophilia would prompt a search for parasitic diseases, vasculitis, or drug reactions.

### ESR

- An elevated ESR suggests the possibility of an underlying systemic disease.

### Urinalysis

- Proteinuria or hematuria may be due to either a primary renal disease or secondary to connective tissue disorder.

### Stools

- To detect ova or cysts of helminthic or protozoal infection.

## INVESTIGATIONS—SPECIFIC

### Challenge Testing for Physical Urticaria

- This may be performed as indicated by patient's history; e.g. test for dermatographism by stroking patient's skin by a blunt, narrow object (tongue blade); pressure urticaria by application of pressure for defined time and intensity; cold urticaria by ice cube test; aquagenic urticaria by challenging with tap water at various temperatures; solar urticaria by exposure to defined wavelengths of light, red cell protoporphyrin, fecal protoporphyrin, and coproporphyrin.

### Throat and Urine Culture

- In patients with history of fever and sore throat for streptococcal infection.

### Multichemistry Screening Panel

- LFTs for evidence of hepatocellular or obstructive jaundice; urea, creatinine, and electrolytes for renal disorders (pyelonephritis, glomerulonephritis, nephrotic syndrome, renal failure); serum glucose for evidence of diabetes mellitus, and serum calcium to screen for malignancy.

### TFTs

- TFTs, including thyroid autoantibodies (antithyroglobulin and antimicrosomal antibodies) may be helpful, given the association of chronic urticaria with Hashimoto's disease, and Graves' disease. Annual reassessment of TFTs in euthyroid patients may be indicated who have elevated antibody titers.

### Serology

- IgM anti-HAV; IgM anti-HBc; HBsAg, i.e. Hepatitis B surface antigen may be present

in acute infection or in patients who are chronic carriers; anti-HCV; and *H. pylori* fecal antigen test.

### Skin Prick Test or Patch Test

- To determine specific allergens responsible for urticaria, anaphylaxis, or food reactions; however, diagnosis of allergy to a specific allergen cannot be made on the basis of testing alone; it requires correlation of the test results with the clinical history.

### Serum Immunoglobulin Analysis

- IgE concentration by RAST and ELISA method may be indicated in patients suspected with allergy due to food, insect bite, or latex allergy. Immunoassay is appropriate for patients in whom skin testing cannot be done (e.g. those who are unable to discontinue use of interfering medications, those who have severe dermatographism or eczema, and those who have had a near-fatal reaction to an allergen).<sup>5</sup>

### Autologous Serum Skin Test (ASST)<sup>6</sup>

- Indicated in all the patients with chronic urticaria because a positive test is suggestive but not diagnostic of an autoimmune basis for the patient's chronic urticaria. Confirmation is needed by *in vitro* testing of the patient's serum for the anti-FCεRIα or the anti-IgE autoantibodies. *In vitro* 'the basophil histamine release assay' is currently the gold standard for detecting functional autoantibodies. However, it is available only at a few research centers and cannot be performed as a routine.

### Serum Complement<sup>1</sup>

- Complement determinations are not indicated for patients who have urticaria alone (since

the values are normal), nor need they be done when angioedema accompanies chronic urticaria, since patients with a hereditary or acquired deficiency of C1 inhibitor do not have hives. Only in patients who present with angioedema alone, as in HAE, is measurement of C4 indicated, followed by a determination of the levels and function of C1 esterase inhibitor, if C4 levels are below normal.

### Cold Agglutinins and Cryoproteins

- In patients with cold urticaria; presence of cryoglobulin suggests chronic hepatitis or malignancy.

### ANA

- May be indicated in patients with chronic urticaria with features of connective tissue disease such as Raynaud's phenomenon, arthralgia, photo sensitivity, and rash.

### Skin Biopsy

- Helpful in patients with urticaria that persist for more than 24 hours; chronic urticaria; or urticaria associated with fever, arthralgia, and elevated ESR suggesting urticarial vasculitis.

### CLINICAL NOTES

- The diagnosis of urticaria is primarily clinical; based on a good history, physical, and systemic examination (Table 45.1)
- History should include enquiry about:
  - Drug exposures (prescription drugs, herbal, and vitamin supplements)
  - Food exposures
  - Physical triggers
  - Infection exposures, especially viral hepatitis

**Table 45.1 : Clinical classification and features of urticaria/angioedema**

<i>Physical urticaria*</i>	<i>Morphology/comments</i>
<ul style="list-style-type: none"> <li>• Dermographic urticaria (rubbing, scratching)</li> <li>• Cholinergic urticaria (sweating due to anxiety, strenuous work, hot bath, alcohol)</li> <li>• Cold urticaria (cold stimuli–wind, drink)</li> <li>• Solar urticaria (sun exposure)</li> <li>• Delayed pressure urticaria (sustained pressure)</li> <li>• Contact urticaria</li> <li>• Urticarial vasculitis</li> </ul>	<ul style="list-style-type: none"> <li>• Linear wheals</li> <li>• Small transient wheals; with surrounding flare; extends from neck to thigh</li> <li>• Small or large wheals; associated with cryopathies</li> <li>• Lesions on photo exposed parts; associated with erythropoietic protoporphyria</li> <li>• Urticaria develops 2-6 hr after pressure, lasts for 12-72hr.; e.g. buttocks (prolonged sitting); waist (tight underclothes); hands (in manual labor)</li> <li>• Induces by biologic or chemical skin contact; e.g. latex sensitivity; cosmetics</li> <li>• Chronic urticaria, frequently lasting &gt;24 hr, more painful than itchy, associated with extracutaneous manifestations such as fever, arthralgia, nephritis, and leaving areas of discoloration as lesions resolve; may be triggered by infection, drugs, or malignant disease; skin biopsy is diagnostic</li> </ul>
<ul style="list-style-type: none"> <li>• Angioedema</li> </ul>	<ul style="list-style-type: none"> <li>• Occurs with or without urticaria; angioedema without urticaria may indicate a C1-esterase inhibitor deficiency, e.g. HAE; commonly involves the lips, eyelids, face, extremities, and genitalia in an asymmetrical manner</li> </ul>

\*defined by the specific physical stimulus.

- Hobbies and occupational exposures
- Travel details
- Insect stings or bites
- Family history of atopy
- Lifestyle, exercise, habits, stress.
- Maintaining daily diet diary and occurrence of skin lesions for fixed duration (2 to 4 weeks), including drugs ingested and activities may be helpful in guiding the etiology. However, it's to be noted that hypersensitivity reactions can develop at any time despite years of uneventful exposure
- Because of the effervescent (i.e. appearance varying in minutes over hours) nature of the urticaria, its features may be difficult to evaluate on a particular occasion. However, careful examination of the skin lesion is important because special forms of urticaria have special features, e.g. dermographism, cold urticaria, cholinergic urticaria, etc
- A comprehensive physical examination of skin, lymph nodes, eyes, joints, throat, neck, ears, lungs, heart, and abdomen can uncover important diagnostic clues that may help diagnose comorbidities such as connective tissue disorders, thyroid disease, and lymphoreticular neoplasms
- The most common cause of acute urticaria is drug reaction; however, up to 50% of cases of acute urticaria a cause is not identified
- A chronic urticaria, frequently lasting more than 24 hours, more painful than itchy, associated with extracutaneous manifestations such as fever, arthralgia, nephritis, COPD, and leaving areas of discoloration as lesions resolve, is suggestive of urticarial vasculitis
- Patients who have both urticaria and angioedema tend to have more severe and persistent disease than patients with only one of the disorders
- Despite a complete examination and extensive laboratory studies, a cause of chronic urticaria is usually not identified.

## RED FLAGS

- Since fatal reactions are known to occur with challenging testes for foods or drugs, they are indicate only in rare cases with compelling reasons to confirm the causative allergen with facilities available for monitoring the patient.<sup>7,8</sup>
- Any patient with tongue edema or edema of the floor of the mouth and laryngeal edema should be hospitalized for airway monitoring.
- Patients with chronic urticaria, suspected to be due to urticarial vasculitis need to be fully investigated for evidence of other autoimmune connective tissue disease or other internal organ involvement.
- Beware of most serious drug reactions such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis.

## SELECTIVE GLOSSARY

**Hereditary Angioedema**—HAE is an autosomal dominant condition caused by a deficiency of the plasma protein C1 inhibitor that afflicts 1 in 10,000 to 1 in 150,000 persons. HAE has been reported in all races, and no sex predominance has been found. It manifests as recurrent attacks of intense, massive, localized edema *without concomitant pruritus*, often resulting from one of several known triggers such as trauma, surgery, dental manipulation, or accidents. However, attacks can occur in the absence of any identifiable initiating event. The most commonly involved viscera are the respiratory and gastrointestinal systems. Involvement of the upper airways can result in severe life-threatening symptoms, including the risk of asphyxiation, unless appropriate interventions are taken. This condition can be differentiated from angioedema in that urticaria does not occur, the lesions are not pruritic, and the lesions are nonresponsive to antihistamines and epinephrine. Historically, 2 types of HAE



have been described—an acquired form of this disorder may also be observed, sometimes in association with an underlying lymphoma. It is important to consider this disorder in the differential diagnosis of unexplained, episodic cutaneous angioedema or abdominal pain. Quantitative and functional analyses of C1 esterase inhibitor and complement components C4 and C1q should be performed when HAE is suspected.

**Sweet's syndrome (Acute febrile neutrophilic dermatosis or acute neutrophilic dermatosis)**—Named after Dr Sweet from Plymouth, England, who first described this condition in 1964, is a reactive process to an internal condition such as URTI, vaccination, pregnancy, IBD, RA, leukemia, internal malignancy, and drugs, e.g. NSAIDs, cotrimoxazole. It may also occur as a result of external triggers such as needle prick, biopsy or insect bite. In some patients they arise only in sun exposed areas, but in others no underlying condition is found. It is characterized by the abrupt onset of tender, red-to-purple papules, and nodules that coalesce to form plaques. The plaques usually occur on the upper extremities, face, or neck and are typically accompanied by fever and peripheral neutrophilia. It most often occurs in middle-aged women, but men, children and the elderly may also be affected. Common symptoms include high or moderate fever; arthralgia; and one or more tender red papules or plaques which enlarge and persist for several weeks, they may have blisters, pustules or ulcers, and sometimes they appear to clear in the center. Sometimes other organs are affected including bones, nervous system, kidneys, intestines, liver, heart, lungs, muscles and spleen. Investigations may reveal: raised ESR or CRP, indicating systemic inflammatory disease; raised WBC count (neutrophil leukocytosis); and numerous neutrophil inflammatory cells on skin biopsy, without leukocytoclastic activity. Sweet's lesions resolve eventually without leaving a mark or scar,

with or without treatment. Sweet's syndrome does not appear to be as rare as it seems though a full blown classical picture may not be observed in each case. Raised, erythematous and painful plaques, particularly if they are asymmetrical, especially in females, should arouse the suspicion of this entity. This is more likely in patients who have underlying malignancy.

**Urticarial vasculitis**—It is thought to be due to immune complex mediated inflammation (i.e. hypersensitivity vasculitis). Although the prevalence of urticarial vasculitis is low, it is nevertheless important to recognize because this disease can be associated with other systemic conditions (e.g. SLE, Henoch-Schönlein syndrome) and is amenable to effective treatment. It is more common in women than in men, and it usually presents in the fourth decade of life. If skin lesions have an urticarial appearance and last longer than 24 hours in the same location, urticarial vasculitis should be considered. Typically these urticarial-like lesions are:

- Less pruritic and more painful than observed with true chronic urticaria
- More prominent on lower extremities
- May be palpable and purpuric
- Following resolution may leave pigmented changes in the skin.

Angioedema may accompany urticarial vasculitis. In addition, urticarial vasculitis may be associated with systemic signs and symptoms such as fever, arthralgia, arthritis, uveitis, episcleritis, hematuria, wheezing, chest pain, and diarrhea. Histopathologic findings include swelling of endothelial cells, neutrophilic perivascular infiltration, extravasation of erythrocytes, leukocyto-clasis (nuclear dust), and fibrinoid deposits around blood vessels. Hemorrhage and edema of the dermis may also occur. The clinical course is usually benign, on average lasting 3 years. The prognosis varies, depending on whether the diagnosis is normocomplementemic urticarial vasculitis



syndrome (NUVS) or hypocomplementemic urticarial vasculitis syndrome (HUVS). NUVS is more benign than HUVS, but both disorders are rarely fatal.

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## CHAPTER

# 46

## Vaginal Bleeding— Abnormal

### SYNOPSIS

Vaginal bleeding, as the term suggests, involves bleeding from the vagina, which may happen to a woman at any stage of her life.<sup>1-3</sup> There are two types of vaginal bleeding. The *normal vaginal bleeding*, with its characteristic features (Table 46.1), called as *menstruation*, which occurs with the onset of ovulation beginning with menarche (between 10-16 years of age), and ends with menopause (between 45-55 years of age).

**Table 46.1:** Characteristics of menstruation

Characteristics	Average	Range
Menarche	12-13 years	10-16 years
Cycle length	26-28 days	21-35 days
Duration of flow	3-5 days	2-7 days
Amount of flow	30-40 ml	10-80 ml
Onset of menopause	47-50 years	45-55 years

*Abnormal vaginal bleeding* (AVB) may be defined as bleeding from the vagina due to a disorder in the vagina or related reproductive organ, particularly the uterus, and which may occur in association with or independent from menstruation. Thus, vaginal bleeding is considered to be abnormal if it occurs:

- When there is a significant deviation from the normal menstrual cycle, i.e. menstruation, and

- At a time when it is not expected, such as before age 10 (precocious menstruation), during pregnancy, or after menopause.

The following terms (Table 46.2) are used to describe AVB related to the menstrual cycle, i.e. abnormal uterine bleeding (AUB), on the basis of its duration, amount, and frequency of the bleeding.

**Table 46.2:** Terminology to describe menstrual dysfunction (AUB)

Term	Definition
Menorrhagia	Prolonged (>5 days) or excessive (>80 ml) menstrual bleeding at regular intervals (21-35 days)
Metrorrhagia	Irregular, frequent menstrual bleeding that is not prolonged or excessive (acyclic bleeding)
Menometrorrhagia	Prolonged or excessive menstrual bleeding at irregular and frequent intervals
Polymenorrhea	Regular menstrual bleeding at intervals of less than 21 days (frequent menses or shortened cycle)
Oligomenorrhea	Menstrual bleeding at intervals of more than 35 days, but less than 90 days (infrequent menses)
Amenorrhea	No menstrual bleeding for 90 days (3 usual cycle lengths) or longer
Intermenstrual	Menstrual bleeding (usually not excessive) between otherwise regular menstrual cycles

Categorizing particular bleeding pattern as defined above is one way of considering cases of AUB. Although each category of menstrual dysfunction has a particular list of causes, necessary testing, and treatment; 'there is no consistent relationship between abnormal bleeding patterns and their causes'.<sup>4</sup> Since AVB can present in many forms, pinpointing the cause for bleeding abnormality can be challenging. However, with the basic knowledge of menstrual physiology, and a thorough approach, the problem can be managed with confidence.

## DIFFERENTIAL DIAGNOSIS

### Common

- Physiologic (ovulatory bleeding, i.e. midcycle ovulation; hypothalamic-pituitary-ovarian immaturity as in perimenarcheal age; transition to premature ovarian failure as in perimenopausal women)
- Dysfunctional uterine bleeding (DUB)\*
- Uterine fibroids
- Complications of early pregnancy (abortion: Threatened, incomplete, complete or missed)
- Ectopic pregnancy
- Pelvic inflammatory diseases (PIDs: STDs, TB endometritis, salpingitis, cervicitis, vaginitis)
- Breakthrough bleeding (BTB) on oral/ injectables contraceptives, HRT
- Benign disorders (cervical or endometrial polyps, cervical erosion, adenomyosis, endometriosis)
- Postmenopausal atrophic vaginitis (endometrial atrophy).

### Occasional

- Complications of late pregnancy (placenta previa, abruptio placenta, premature labor, subinvolution of the placental site)

\*DUB is a symptom complex that includes any condition of AUB in the absence of pregnancy, neoplasm, infection, and other pathology of the female genital tract as well as other systemic cause of abnormal bleeding.

- Endocrine (Hypothyroidism, hyperthyroidism)
- Trophoblastic disease
- Postcoital bleeding.

### Rare

- Malignancy (endometrial, cervical, ovarian, vulvar, vaginal, secondary tumors)
- Metropathia hemorrhagica (Cystic glandular hyperplasia)
- Choriocarcinoma
- Liver, renal disorders
- Endocrine (PCOS, Addison's disease, Cushing's syndrome, prolactinoma)
- Bleeding disorders (von Willebrand's disease, thrombocytopenia, leukemia, hemophilia, thalassemia)
- Drugs (anticoagulants, NSAIDs)
- Foreign bodies (forgotten tampon, IUDs).
- Traumatic lesions (sexual abuse, domestic violence, rape, ruptured hymen).

## INVESTIGATIONS—GENERAL

### Pregnancy Test

- If premenopausal, urine  $\beta$ -hCG; if ectopic pregnancy is suspected serum  $\beta$ -hCG-pregnancy test will be more definitive.

### CBC

- Hemoglobin—Low Hb in chronic AUB; however, a patient may have normal Hb and hematocrit in spite of a heavy menstrual flow. Excess menstruation may result in iron deficiency, but iron deficiency anemia is a late manifestation of excessive menstrual flow. Therefore, a history of excessive menstrual flow should not be discounted simply on the basis of normal hemoglobin value
- Leukocytosis in PID
- Thrombocytopenia in bleeding disorders.

### Coagulation Profile

- Platelet count, PT, PTT, bleeding time.

### Blood Sugar

- Diabetes mellitus is a risk factor for endometrial carcinoma, and women with PCOS have been recognized to have an increased incidence of diabetes mellitus (and adverse cardiovascular events which constitute 'metabolic syndrome').

### Pap Smear

- To screen for cervical cancer, cervicitis.

### Cervical Culture

- For gonococcal, trichomonas, and chlamydial infection.

### Thyroid Function Test

- TSH, FT4, for possible thyroid dysfunction in patients suspected with anovulatory cycles.

## INVESTIGATIONS—SPECIFIC

### Pelvic US

- To detect uterine and ovarian abnormalities (bicornate uterus, tumors, PCOS), hydatidiform mole, and to establish the cause of bleeding in pregnancy.

### Transvaginal Ultrasound (TVUS)

- Invaluable in the initial evaluation in women at low risk for endometrial cancer. Adnexa, ovaries, fibroids, and the endometrium for its thickness (i.e. endometrial echo) can be assessed to decide whether the patient requires further evaluation with saline infusion sonography (SIS) and hysteroscopy. Normally the endometrial echo measures less

than 5 mm. Increased endometrial thickness is associated with endometrial hyperplasia, endometrial polyps, fibroids, and endometrial cancer. When the endometrial echo is greater than 5 mm, or is indistinct or indeterminate, an enhanced view is required with SIS or hysteroscopy. An endometrial echo of less than 5 mm is associated with malignancy in less than 0.5% of cases.

### Saline Infusion Sonography (SIS): Conventional and 3D-SIS

- To diagnose intracavitary lesions, endometrial hyperplasia, and carcinoma. Current indications for SIS include:
  - Abnormal bleeding in premenopausal or postmenopausal patients;
  - Evaluation of an endometrium that is thickened, irregular, immeasurable, or poorly defined on conventional TVUS;
  - Irregular-appearing endometrium with TVUS in women using tamoxifen;
  - The need to differentiate between sessile and pedunculated masses of the endometrium; and
  - Presurgical evaluation of intracavitary fibroids.
- "SIS is a simple and elegant examination that yields additional information over TVUS of the uterus. Because the walls of the endometrium are separated by SIS, they can be evaluated individually. Focal abnormalities are beautifully displayed by this technique. This information can then be used to direct the intervention. Biopsy of diffuse abnormalities can be performed with a blind technique, whereas focal abnormalities are best approached with a visually guided biopsy. SIS requires minimal patient preparation, has very few complications, and is well-tolerated by patients. Given its advantages over other techniques for uterine evaluation, SIS will

likely play an even larger role in pelvic imaging in future.”<sup>5</sup>

- Further, three-dimensional saline infusion sonography (3D SIS) is found to be valid and reliable in women suspected of having intrauterine abnormalities, and may indeed have relevant clinical value in addition to conventional SIS.<sup>6</sup>

### **Hysteroscopy**

- Flexible hysteroscopy allows direct visualization of the endometrium and it can be used for directed biopsy and removal of small polyps.

### **Coagulation Profile**

- von Willebrand panel, including von Willebrand antigen and ristocetin cofactor assay, and other tests for intrinsic qualitative platelet disorders are indicated in adolescents and in patients with family history of bleeding diathesis if a bleeding disorder is highly suspected.

### **Serum Progesterone**

- To determine ovulatory or anovulatory status
- In ovulatory cycles—preovulatory serum progesterone values are <1 ng/ml; and post-ovulatory serum progesterone values are >5 ng/ml
- In anovulatory cycles, serum progesterone values never exceed 5 ng/ml.

### **LH, FSH**

- Ratio of LH: FSH >3 indicates PCOS; FSH >40 U/ml indicates imminent ovarian failure.

### **Prolactin (PRL)**

- Hyperprolactinemia needs to be ruled out in women with anovular cycles.

### **Serum Testosterone, Free Testosterone, 17-Hydroxyprogesterone**

- In women with hyperandrogenic symptoms and signs – serum testosterone > 60 ng/dl supports the diagnosis of PCOS
- If serum testosterone > 150 ng/dl, then 17-hydroxyprogesterone estimation is indicated to rule out functional adrenal or ovarian neoplasm.

### **Urinary Gonadotropins**

- High titers in trophoblastic disease like hydatidiform mole (molar pregnancy) or choriocarcinoma.

### **Abdominal CT Scan**

- To evaluate for adrenal or ovarian tumor in women with hyperandrogenic symptoms and signs with elevated serum testosterone and DHEA-S.

### **MRI of Pituitary**

- To detect adenoma; prolactinomas are the most common hormone-secreting pituitary adenomas.

### **Endometrial Biopsy (EMB)**

- EMB is indicated in women older than 35 years of age who have AUB associated with increased risk factors for endometrial hyperplasia and endometrial cancer. Biopsy is also indicated for patients aged 18 to 35 years with risk factors for endometrial cancer. Risk factors include:
  - Obesity
  - Diabetes mellitus
  - Infertility
  - Chronic anovulation (anovulatory for at least 1 year)
  - Postmenopausal, not on HRT

- New onset AUB in postmenopausal woman on HRT
- Suspected PCOS
- Tamoxifen therapy.

### CLINICAL NOTES

- Confirm source of vaginal bleeding—uterine or extrauterine. It is not uncommon for a woman to be unaware of the exact source of an unexpected and AVB. She may just complain that she has noticed blood on her undergarments or on the tissue paper after wiping external genitalia and that she cannot find a reasonable explanation for such abnormal bleeding—it being significantly different from her previously established pattern of menstrual flow. Therefore, the first and foremost thing to do is to obtain careful history to ascertain that the blood is flowing from the vagina, and not from the rectum or mixed with urine (i.e. associated with bowel movements or urination), thus focusing on genital etiologies, predominantly uterine (AUB). Examination of stools for the presence of blood (hematochezia) and urine (hematuria) is helpful to differentiate between vaginal (i.e. uterine) and extrauterine (i.e. gastrointestinal or genitourinary) causes of AVB
- Rule out or confirm pregnancy, if premenopausal—Because bleeding can indicate a complicated pregnancy, possible pregnancy should always be considered in a woman of child-bearing age. Spotting to minimal bleeding may be normal, but any bleeding during pregnancy needs to be evaluated. Heavy bleeding before 12 weeks may indicate serious problem, including abortion (threatened, incomplete, and missed), molar pregnancy, or ectopic pregnancy; and that occurring after 12 weeks may be due to placenta previa
- In premenopausal women—is the bleeding ovulatory or anovulatory? Normal ovulation is necessary for regular menstrual cycle; a distinction between ovulatory and anovulatory bleeding is critical because causes and therapies are distinct (Tables 46.3 and 46.4)
- All women with evidence of severe bleeding on physical examination (e.g. pallor, hypotension) should be fluid resuscitated and emergently hospitalized.

**Table 46.3:** Differentiation of ovulatory and anovulatory cycles

Criteria	Ovulatory cycles	Anovulatory cycles
History	Regular cycle length; Ovulation pain (mittelschmerz); Premenstrual molimina (breast soreness, bloating—fluid retention, weight gain, and mood change), dysmenorrhea (cramps, back pain)	Prolonged bleeding at irregular intervals after not having a menstrual period for several months; subjective symptoms preceding the cycles are absent
Cervical mucus	Preovulatory cervical thin mucus discharge is usually observed halfway between menstrual cycles	
Basal body temperature record	Biphasic pattern	Monophasic pattern
Serum progesterone level	Preovulatory < 1 ng/ml Postovulatory > 5 ng/ml	Never exceeds 5 ng/ml; usually preovulatory values
Premenstrual endometrial biopsy	Secretory endometrium	Proliferative and possibly hyperplastic changes
Common examples	Physiologic normal variants; fibroid, polyps, PID, systemic disorders	DUB, hypothalamic dysfunction—secondary to stress, depression, eating disorders, obesity; adolescence; BTB; endometrial hyperplasia



**Table 46.4:** Differential diagnosis of abnormal vaginal bleeding (AVB)

Ovulatory bleeding	Physiologic: Midcycle ovulation (Mittelschmerz) Anatomic lesion: Fibroids; PID; cervical-infection, polyp, cancer; IUD Systemic disease: Bleeding diathesis; hepato-renal disorder Local disorders: Foreign body; trauma; infection; urethral prolapse; growth
Anovulatory bleeding	Hypothalamic dysfunction: Premenarcheal perimenopausal; stress, weight loss, heavy exercise Excess androgen, prolactin, cortisol Hypothyroidism PCOS Oral contraceptive use: Inadequate estrogen dose
Postmenopausal	Endocrine pathology: Fibroid; polyp; cancer Cervical pathology: Erosion; polyp; cancer Vaginal pathology: Atrophic vaginitis
Pregnancy	Early pregnancy: Abortion: Complete; incomplete; inevitable; missed Late pregnancy: Placenta previa; abruptio placenta; Retained products of gestation Ectopic pregnancy

- The history should determine the following information:
  - *Age of onset of bleeding, age of onset of puberty.* Though premenarchal bleeding may be associated with precocious puberty, local pathology, as well as adrenal and ovarian tumors must be ruled out. In adolescence, AUB is common in the first 2-3 years after menarche due to many anovulatory cycles,

resulting in irregular, heavy menses and probably dysmenorrhea. Once ovulation and menstruation are regularly established, the cycle follows a predictable pattern (Table 46.1) and any deviation can be considered as AUB.

- *Menstrual history*—The *first day* of last menstrual period should be included in all adult female patients, i.e. the date that the menstrual flow began. Many patients assume that occurrence of any bleeding is a 'period'. Also, for many women, monthly may mean once every calendar month, so that a period on day 1 and day 27 of the same month, while normal, may strike her as having periods twice a month. Failure to make this distinction can result in misleading information. A menstrual calendar<sup>†</sup> (over three or more months) can be a very useful guide. The quantity (the passage of 'clots' or inability to control bleeding with tampons is significant and indicates heavy bleeding), duration, and frequency of bleeding<sup>‡</sup> with respect to previous menstrual cycles are recorded. Any significant deviation from normal should be noted and patient's cycles are categorized as in Table 46.2.
- Postcoital bleeding (any bleeding after intercourse or in association with douching) is suggestive of cervical dysplasia, or endocervical polyps.
- Postmenopausal bleeding (any bleeding occurring in a postmenopausal woman at least 1 year after cessation of cycles) should be evaluated for endometrial hyperplasia and carcinoma.

<sup>†</sup>Visit web site -<http://www.americanpregnancy.org/gettingpregnant/ovulationcalendar.html>

<sup>‡</sup>It is not uncommon for women to change their sanitary products frequently for hygienic reasons or because of personal preference or concern for toxic shock syndrome than because of heavy flow.

- *Associated symptoms*—Pain, discharge, fever, nausea, vomiting, dysuria; symptoms of hyperthyroidism (fatigue, weight loss, sweating, palpitation); hypothyroidism (fatigue, cold intolerance, constipation); symptoms of hyperprolactinemia (headache, nipple discharge, galactorrhea); symptoms of virilization (excess hair growth); bleeding diathesis (easy bruisability, petechiae, epistaxis, gingival bleeding); etc. should be addressed
- *Sexual history*—Sexual abuse and activity, including high risk behavior, and domestic violence screening is recommended
- *Personal and family history*—Marital status, parity, infertility, epilepsy, and blood dyscrasia. Smokers have higher incidence of menstrual dysfunction
- *Medications*<sup>§</sup>—Oral contraceptives, anticoagulants antidepressants, antiepileptics, antipsychotics, opiates, Tamoxifen, and herbal preparations (ginseng, ginkoba, soya supplements)
- *Physical examination*—Evidence of puberty (breast development, axillary and pubic hair growth); virilization, hirsutism; hypothyroidism (dry skin, coarse hair, bradycardia, delayed reflexes); hyperthyroidism (sweating, weight loss, palpitation); abdominal distension, tenderness, hepatomegaly, splenomegaly; skin petechiae; etc.

### Pelvic Examination

- Inspection of genitalia—Anatomy, discharge, foreign body, evidence of trauma, and source of bleeding—uterine or extra-uterine.
- Other lesions—Polyps, fibroids, pelvic mass.

- Pap smear and biopsy of any lesion in the genital tract.

### Digital Rectal Examination (DRE) and Proctoscopy

- May be warranted to identify alternative sources of bleeding such as rectal or urethral.

### RED FLAGS

- In a woman of reproductive age, pregnancy should always be ruled out despite a negative history of sexual activity
- AUB in a woman of reproductive age must be considered a complication of pregnancy until proved otherwise
- Vaginal bleeding in a postmenopausal woman must be considered a malignancy until proved otherwise
- Reevaluate patients diagnosed with hyperplasia with atypia for persistent or worsening hyperplasia within 3-6 months of treatment
- Vaginal bleeding that occurs before pubertal development or normal menarche should raise suspicion of nonendocrine causes; rule out adrenal and ovarian tumor, including rhabdomyosarcoma (sarcoma botryoides)
- AUB during adolescence should be attributed to a coagulation disorder until proven otherwise
- AUB before menarche may warrant pelvic examination under general anesthesia to exclude focal lesions such as trauma, sexual abuse or assault, and malignancy
- Any AVB/AUB should be investigated in women taking Tamoxifen or Raloxifene because the resulting side effects of these drugs (indicated in breast cancer) include an increase in the risk of endometrial cancer and thrombosis.

<sup>§</sup>Common medications, which increase the cytochrome P450 enzymatic processes in the liver, may induce more rapid metabolism of steroid hormones, thereby decreasing their bioavailability and result in AUB that is secondary to a relative insufficiency of estrogen or progesterone.

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## CHAPTER

# 47

## Vertigo

### SYNOPSIS

*Vertigo* can be defined as a hallucination of an abnormal sensation of rotation or imbalance of either the self or the surroundings (e.g. rotating, spinning, tilting, and swaying). Patients may feel that they are moving while the surroundings remain still (*subjective vertigo*), or that the surroundings move while they are stationary (*objective vertigo*), or that both they and the surroundings are in motion.\* It is usually associated with headache, pallor, sweating, nausea, vomiting, hyperventilation and imbalance. The patient tends to keep his head immobile out of fear of a fresh attack and is disinclined to walk, especially in crowded surroundings.

In practice, however, it is unusual for patient to complain of vertigo, i.e. the majority do not present solely with true spinning vertigo—that they are moving relative to the surroundings, or that the surrounding is moving, and that the symptoms are (or not) provoked by head movements when they are at rest, sitting or lying down. Most commonly patients complain of symptoms suggestive of *presyncopal* episode,

\* The distinction between subjective and objective vertigo is probably of not much localizing value.

such as giddiness<sup>†</sup>, dizziness, fainting; or symptoms of *disequilibrium*, such as inability to maintain normal gait and normal posture (Table 47.1). Therefore, the words that patients use to describe their symptoms of 'vertigo' are significant because a number of seemingly synonymous terms often relate to distinct physiological mechanisms.

The five sensory modalities which constantly monitor position and motion are: Vision, vestibular end organs, proprioception, touch and pressure, and cerebellum. Normally the brain integrates the input from each of these sensory modalities giving a comprehensive image of position and motion in space. This process enables us to maintain balance, move about, and interact with other objects. However, pathology affecting the central nervous system, eyes, ears, locomotor system, and other systems such as hemopoietic system, cardiovascular and endocrine systems may all alter the delicate

<sup>†</sup>Giddiness is an unpleasant sensation of disturbed relation to surrounding objects in space. Dizziness, however, is an imprecise term, generally used collectively to describe all types of equilibrium disorders, including giddiness, light-headedness, imbalance, ataxia, vertigo, or minor episodes of mental confusion.

**Table 47.1:** Causes of dizziness

<i>Symptom description</i>	<i>Characteristics</i>	<i>Possible etiologies</i>
Vertigo: Spinning or whirling; “like getting off a merry-go-round”; “the ground tilts up and down; like being on a boat at sea”.	Illusion of motion of self (subjective) or environment (objective)	Dysfunction of vestibular system—peripheral or central
Disequilibrium: Poor balance, but not dizzy; “the problem is in my legs”.	Impaired balance or coordination; unsteady gait	Cerebellar lesion; brainstem lesion; extrapyramidal disorder; bilateral vestibular dysfunction; peripheral neuropathy
Presyncope: Lightheadedness; fainting; “I feel like I will pass out”.	Patient senses <i>impending</i> loss of consciousness; often with systemic symptoms—nausea, diaphoresis, dimness of vision, blackout; inciting event	Cerebral hypoperfusion—causes numerous
Multiple sensory deficit: “I am unsteady on my feet”; “I am afraid I will fall”.	Often elderly people afflicted by a variety of ills that summate to impair the patient’s ability to ambulate unassisted; dramatically improved by the use of a cane or the supporting arm of a companion	Multiple concurrent problems; visual impairment, deafness, peripheral neuropathy, painful or disabling orthopedic disorders, and muscle weakness
Ill defined	Histrionic but vague description; nonspecific complaints	Psychogenic

balance of neural information resulting in disequilibrium and vertigo. Hence, proper understanding of etiopathology, i.e. central (brain) or peripheral (inner ear, 8th cranial nerve); coupled with systematic, efficient and formal evaluation is required in order to provide appropriate management and rehabilitation.

## DIFFERENTIAL DIAGNOSIS

### Common

- Physiological (motion sickness)
- Positional vertigo (vertebrobasilar ischemia, cervical spine dysfunction, or benign paroxysmal positional vertigo, i.e. BPPV)
- Vestibulopathy (vestibular neuronitis, labyrinthitis, herpes zoster)
- Vascular (subarachnoid hemorrhage, vertebrobasilar ischemia, brainstem infarct, cerebellar infarct, lateral medullary syndrome, i.e. PICA syndrome: *vide infra* ↓↓)

- Ménière’s syndrome (*vide infra* ↓↓)
- Migraine (aura, basilar migraine)
- Multiple sensory deficit syndrome<sup>†</sup> (*vide infra* ↓↓)
- Systemic disorders (hypotension, cardiac arrhythmia, hypoglycemia)
- Psychogenic (hyperventilation, anxiety, panic attack, agoraphobia, somatization, conversion, depression).

### Occasional

- Ototoxic drugs (aminoglycoside antibiotics, aspirin, frusemide, phenytoin, quinine)
- Epilepsy (aura in temporal lobe epilepsy)
- Physical (barotrauma, noise trauma)
- Head injury (posttraumatic labyrinthine concussion, perilymph fistula).

<sup>†</sup>This term usually refers to elderly persons who often have altered sensory inputs or premature aging of the vestibular nuclei.

**Rare**

- Cerumen impaction (common but rare cause of vertigo)
- Neoplastic (acoustic neuroma, vide infra↓↓, tumors of brainstem, and floor of IVth ventricle)
- CNS degenerative disease (MS, cervical OA, syphilis)
- Endocrine disorders (hypothyroid, adrenal insufficiency)
- Post-ENT surgical status (stapedectomy, tympanoplasty)
- Hereditary (otosclerosis).

**INVESTIGATIONS—GENERAL****CBC**

- Elevated WBC counts in infection. Elevated hematocrit (polycythemia) predisposes to CVA. Decreased Hb% in anemia.

**ESR**

- May be elevated in bacterial infection, TB, and malignancy.

**INVESTIGATIONS—SPECIFIC****Audiometry**

- Pure tone audiogram, speech discriminating testing, and tympanometry performed in all patients with significant hearing loss or tinnitus; valuable in differentiating labyrinthine rather than cerebral cortex or brainstem lesions as the cause of vertigo.

**CT Head**

- Indicated in patients with head trauma to identify fractures and CVA.

**MRI and Angiography**

- Acoustic neuroma and other CP angle tumors; acute vertigo with risk factors for

stroke, cerebellar hemorrhage or infarction; and multiple sclerosis.

**Brainstem Evoked Response (BSER)**

- Useful screening test in patients with suspected central causes of vertigo. A normal BSER safely excludes an acoustic neuroma. If BSER is abnormal, an imaging procedure, such as MRI, is indicated.

**Carotid Doppler Ultrasound**

- To evaluate patency of the vessels and to screen for evidence of plaque precipitating TIAs.

**ECG/Holter Monitor**

- To screen for arrhythmia.

**EEG**

- In suspected cases of complex partial seizure.

**X-ray Cervical Spine**

- May be useful in demonstrating vertebral foraminal encroachment, which sometimes compromises arterial blood flow to the brainstem and the peripheral auditory apparatus.

**CLINICAL NOTES**

- Since classifying patient's complaints of vertigo is made specifically on the basis of a careful history, it is important to ask the patient to describe symptoms in detail. It will then become apparent whether the patient is suffering from vertigo or other similar symptoms. Important historical information include:
  - The symptoms in the patient's own words (is it vertigo or something else?)
  - Onset, duration, episodic or continuous condition.



- Is vertigo central, peripheral origin, or general medical cause?
- Is vertigo due to urgent causes or non-urgent causes?
- Are there any correctable underlying diseases?
- Hearing loss, imbalance, aural fullness, tinnitus (as in Ménière's syndrome).
- Aura, headache, diplopia, dysarthria (central causes).
- Aggravating factors (as with head movement, postural change, travel, noise, exercise).
- Recent head trauma or viral upper respiratory infections (as in perilymph fistula, vestibular neuronitis).
- Past history of similar attacks or risk factors for atherosclerosis.
- Is it a psychogenic vertigo?
- Does it need ENT or neurology consult?
- The points which help determine *true vertigo* are:
  - Element of rotation.
  - Associated with nystagmus, ataxia, nausea, vomiting.
  - Attack reproduced by rapid head movements.
- Past medical history of aural infection, head injury, diabetes, hypertension, CAD, CVA, migraine, epilepsy,<sup>1</sup> or psychiatric disorders are helpful in the diagnostic evaluation
- All past and present medications should be assessed with particular attention to aminoglycoside antibiotics, anticonvulsants, antihypertensives, and high dose salicylates
- Important bedside examinations for vertigo include:
  - Detection of spontaneous nystagmus.
  - Barany rotation (head-shaking nystagmus—horizontal and vertical).
  - Dix-Hallpike (Nylen-Barany) maneuver.
  - Valsalva-induced nystagmus (closed glottis, pinched nostrils).
  - Hyperventilation-induced nystagmus.
  - Romberg test, Fukuda test.
  - Finger-nose (past-pointing) test.
- Detection of *nystagmus* is critical because it is the only objective sign of vertigo. Nystagmus can occur spontaneously or in response to changes in eye or body position. Peripheral vestibular disorders usually cause horizontal or rotatory nystagmus, whereas brain-stem disorders are reflected by vertical nystagmus
- *Vestibular testing.* The most common and useful test is the *Bárány or Dix-Hallpike maneuver*. The patient is asked to turn his head. A rapid change in position from sitting to supine (with head hanging over the edge of the examination table) will produce active rotatory nystagmus when head is turned so that the affected ear is facing the floor. This may be accompanied by nausea
- *Weber's and Rinne's test* help in differentiating conductive loss from sensory neural hearing loss. Conductive hearing loss is seen in cases of otitis media and early stages of Ménière's disease, while sensory neural hearing loss is seen in ototoxicity and tumors of the auditory nerve
- Cerebellar dysfunction can be evaluated initially by observing the gait, *Romberg test*, *Fukuda test*, and *finger-nose test*<sup>§</sup>
- Cardiovascular examination with special emphasis for orthostatic changes in BP, carotid bruits, murmurs and arrhythmias is helpful in selected cases
- Neurological examination includes evaluation of cranial nerves, in particular *fundoscopy*

<sup>§</sup>Ref. Chapter 21 Gait disorders. p. 138

for papilledema or optic atrophy (II), ocular movements (III, IV, and VI), corneal reflex\*\* (V), and facial movements (VII)

- *Otoscopy* can detect otitis media, serous otitis or cholesteatoma
- Onset and duration—Generally, central vestibular disorders, i.e. *central vertigo*, are characterized by gradual and insidious onset of continuous imbalance, whereas a peripheral vestibular disorder, i.e. *peripheral vertigo*, is classically characterized by sudden, short lived (of few hours) episodes of vertigo (Table 47.2).

**Table 47.2:** Vertigo: Causes and onset of attack

*Acute*

- CVA, TIA: vertebrobasilar event; subarachnoid hemorrhage; cerebellar infarct
- Head trauma, concussion
- Infections – otological – vestibular neuronitis
- Tumor
- Seizure

*Recurrent*

- CVA, TIA
- Ménière's disease
- Tumor
- Migraine
- Seizure
- Toxic – drugs, substance abuse
- Multiple sclerosis
- Syphilis
- Surgery/otological/ENT procedures
- Psychogenic

*Positionally provoked vertigo*

- Benign positional vertigo
- Cervical sprain, OA, whiplash injury
- Vascular—Anterior vestibular artery occlusion, verte-brobasilar artery insufficiency
- Postsurgical (head/neck/ENT) status
- Central cause

- Age—In young adults psychological causes predominate, whereas vestibular disorders do in the middle age. In the elderly, cerebrovascular and cardiac disorders, combined with *multiple sensory deficits*

outweigh vestibular causes. Therefore, in the elderly, it is more sensible to consider vertigo (along with other conditions which frequently accompany it) as part of a more general syndrome<sup>2</sup>

- In an elderly sudden onset of severe vertigo, headache, nausea and vomiting, usually associated with other neurological symptoms, such as diplopia, dysphasia, hemiparesis—but without hearing loss or tinnitus—is strongly suggestive of verte-brobasilar insufficiency
- Sudden, episodic vertigo, associated with progressive unilateral hearing loss and tinnitus, lasting from hours to days is suggestive of Ménière's disease
- Vertigo precipitated by positional factors, i.e. vertigo on arising from supine to sitting or standing position; vertigo with sudden neck movements, accompanied by nystagmus, but without hearing loss, is suggestive of cervical spine dysfunction, vascular ischemia, or BPPV
- Mild vertigo (vague sensation of motion) with prominent tinnitus, progressive unilateral sensorineural hearing loss, and loss of corneal reflex strongly suggests cerebellopontine angle tumor—usually acoustic neuroma
- Vertigo with multiple neurological signs and symptoms, such as blurring or loss of vision, diplopia, dysarthria, paresthesia, and ataxia is suggestive of multiple sclerosis (vide infra ↓↓)
- Vertigo that is increased by a loud noise (Tullio phenomenon, i.e. vestibular hypersensitivity to sound) and Valsalva maneuver suggests perilymphatic fistula
- Organic vertigo is accompanied by nystagmus; a psychogenic etiology is almost certain when nystagmus is absent during a vertiginous episode.

\*\* Abnormal or absence of corneal reflex on the affected side may be the first signs of CP angle tumors.

## RED FLAGS

- In elderly age group patients with risk factors for stroke, possibility of vascular vertigo should always be considered in both acute prolonged vertigo and recurrent vertigo
- In a patient with acute vertigo, it is important to distinguish vestibular neuronitis from an *inferior cerebellar infarction*. A stroke involving the inferior cerebellum can be a neurosurgical emergency marked by cerebellar swelling and brainstem compression. Patients with cerebellar infarct are unable to stand or walk. This is the main distinguishing feature from vestibular neuronitis
- Majority of cerebellar infarct patients have a cardiac source of embolism, requiring specific cardiac evaluation and management.

## SELECTIVE GLOSSARY

**Acoustic neuroma (AN)**—It is also known as *vestibular schwannomas*, and are nonmalignant tumors of the 8th cranial nerve. Most commonly they arise from the Schwann cell investment of the vestibular portion of the vestibulocochlear nerve. Less than 5% arise from the cochlear nerve. As the tumor expands, it projects from the internal auditory meatus into the cerebellopontine angle and compresses the cerebellum and brainstem. The 5th cranial nerve and later the 7th cranial nerve are affected. AN occurs in two forms—a sporadic form, and a form associated with an inherited syndrome called neurofibromatosis type II (NF2). About 95% of all cases are sporadic. Clinical manifestations include hearing loss, headache, vertigo, tinnitus, and facial pain. Unilateral sensorineural hearing loss – sudden, progressive, or fluctuating – is the most common symptom present at the time of diagnosis. Vertigo, dysequilibrium, headaches, facial numbness or facial weakness are uncommon presenting symptoms among patients with AN. A significant number of patients with AN present atypically,

with none of the audiovestibular symptoms classically associated with AN. Clinician awareness of the atypical clinical symptoms may lead to earlier detection of these lesions.<sup>3</sup> Further, the natural history of AN is yet not totally known, but most of them have the tendency to slow growth, sometimes without any kind of symptoms during the individuals entire time.<sup>4</sup> Considering ANs natural history, there is a possibility for conservative treatment for these tumors.

The definitive diagnostic test for patients with ANs is gadolinium-enhanced MRI. Gadolinium contrast is critical because nonenhanced MRI can miss small tumors. If suspicion is high, and MRI is contraindicated, air-contrast cisternography has high sensitivity and can detect relatively small intracanalicular tumors.

**Ménière Disease**—Ménière's syndrome is a disease of the inner ear (resulting from non-suppurative disease of the labyrinth) that is characterized by attacks of severe vertigo, tinnitus, fluctuating hearing loss, and ill-described aural sensations of fullness with spontaneous recovery in hours to days. Ménière's disease usually develops between the ages of thirty and fifty, and is slightly more common in women than in men, and in 50% of Ménière's patients become bilateral. The most consistent pathological finding in Meniere's syndrome is an increase in the volume of the endolymphatic fluid and distension of the canals, hence the term *endolymphatic hydrops*. Although some specific causes such as bacterial, viral, and syphilitic infections may lead to the same pathological changes and symptoms, the majority of cases are idiopathic. The prognosis is for progressive reduction in hearing along with increasing frequency of attacks. Some patients stabilize with no subsequent attacks of severe vertigo, but they are left with residual hearing loss.

**Multiple Sclerosis (MS)**—An idiopathic inflammatory demyelinating disease of the CNS, mainly affecting young adults, and characterized by destruction of myelin in the central nervous system. Patients with MS commonly present with an individual mix of neuropsychological dysfunction, which tends to progress over years to decades. Clinical manifestations include visual loss, extraocular movement disorders, and paresthesias, loss of sensation, weakness, dysarthria, spasticity, ataxia, and bladder dysfunction. The usual pattern is one of recurrent attacks followed by partial recovery. The diagnosis of MS is based on a classic presentation (i.e. optic neuritis, transverse myelitis, internuclear ophthalmoplegia, paresthesias), and on the identification of other neurologic abnormalities, which may be indicated by the patient's history and examination. Typical findings on an MRI also help to establish the diagnosis of MS. Patients with atypical pre-presentations and/or a normal or atypical MRI may require evoked potential studies, to uncover subclinical neurologic abnormalities, or cerebral spinal fluid (CSF) analysis, which also serves to exclude treatable disorders and document MS-like immune activity in the CNS.

**Multiple Sensory Deficit Syndrome**—This term usually refers to elderly persons who often experience dizziness as a result of altered sensory inputs or premature aging of the vestibular nuclei. Visual impairment (cataracts), deafness (presbycusis), decreased ability to feel their legs (peripheral neuropathy), painful or disabling orthopedic disorders, and muscle weakness collectively alter the patient's perception of space, fluidity of motion, and confidence in walking,

resulting in difficulty with activities of daily living and even falls. Medication is usually not helpful unless there is clear vertigo due to inner ear dysfunction. However, Patients can be helped by increasing their sensory input by using a cane, not to support a weak leg, but by dragging it along the ground, which increases sensory input through the arm where the cane is held. The individual has a better sense of stability and 'where the ground is', and many times can walk more steadily and safely.

**PICA (Posterior inferior cerebellar artery) Syndrome**—The PICA syndrome, also known as *lateral medullary syndrome*, or *Wallenberg's syndrome*, is the most common brainstem stroke. It is typified by vertigo, ipsilateral hemiataxia, dysarthria, ptosis and miosis. Patients often have Horner's syndrome (unilateral ptosis, miosis and facial anhidrosis). There also may be saccadic dysmetria (overshoot), saccadic pulsion (pulling of the eye during vertical saccades toward the side of lesion). Diagnosis is generally via MRI. Prognosis is generally good with full or near full recovery expected at 6 months.

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## CHAPTER

# 48

## Vision Loss—Gradual

### SYNOPSIS

As the world population ages, vision loss is becoming a major public health problem. Researchers for the Johns Hopkins Bloomberg School of Public Health, and the London School of Hygiene and Tropical Medicine found that, without extra intervention, the global number of blind individuals would increase from 44 million in 2000 to 76 million in 2020.<sup>1</sup> Therefore, any type of vision loss, low vision, or visual impairment (e.g. blurred vision, double vision, night blindness, loss of central or peripheral vision) is a symptom of great concern to everyone.

*Vision loss* means that a person's eyesight cannot be corrected to normal level, making it difficult or impossible to do daily tasks without glasses, contact lenses, surgery, or other assistance. This can lead to loss of independence and reduced quality of life. This type of vision loss does not include complete blindness, because there is still some sight and it can sometimes be improved with the use of visual aids.

WHO defines a person with low vision as:

*"One who has impairment of visual functioning even after treatment and/or standard refractory correction, and has a visual acuity in the better eye of less than*

*6/18 to light perception, or a visual field of less than 10 degree from the point of fixation, but who uses, or potentially able to use, vision for the planning or execution of a task."*<sup>2</sup>

However, to allow comparison with other studies, the commonly used WHO classification (Snellen) of low vision as: "best corrected visual acuity < 6/18 to 3/60, and blindness as best corrected visual acuity < 3/60 to NPL, i.e. no perception of light" is generally used.

In order to facilitate the screening of visual acuity by nonstandardized personnel, in the absence of appropriate vision charts, the WHO has now added, "inability to count fingers in daylight at a distance of 3 meters", to indicate less than 3/60 or its equivalent visual impairment.<sup>3</sup>

Many causes of vision loss are very serious medical conditions, requiring immediate or urgent care, where delay can lead to loss of vision, e.g. retinal detachment, or loss of life, e.g. occipital stroke. Even transient blindness or loss of vision cannot be ignored because it can result from serious conditions such as TIA, hypertension, diabetes mellitus, and epilepsy. Therefore, the key to successful diagnosis lie in the history, age of the patient, and the pattern of field loss, backed up by an examination of the eye through a dilated pupil.



## DIFFERENTIAL DIAGNOSIS (TABLE 48.1)

### Common\*

- Senile cataract
- Chronic glaucoma
- Diabetic maculopathy
- Hypertensive retinopathy
- Age-related macular degeneration (ARMD)
- Gradual inferior retinal detachment
- Chronic papilledema
- AIDS (CMV retinitis).

**Table 48.1:** Causes of progressive bilateral vision loss

Site of lesion	Examples
Ocular Retina	Chronic glaucoma; senile cataract ARMD; retinal disease, e.g. diabetic retinopathy, hypertensive retinopathy, retinitis pigmentosa, choroidoretinitis
Optic nerve	Optic neuropathies; optic nerve compression, e.g. glioma, aneurysm
Optic chiasma	Chiasmal compression, e.g. pituitary tumor, craniopharyngioma
Occipital cortex	Tumors; degenerative conditions

### Occasional

- Optic nerve compression (mass lesion)
- Intracranial tumors
- Intraorbital tumors
- Retinitis pigmentosa
- Complications of cataract surgery (inflammation, retinal detachment, posterior capsular fibrosis).

### Rare

- Toxic amblyopia (drugs/toxins – alcohol, anticholinergic agents, amiodarone, corticosteroids, chloroquin, digoxin, ethambutol, isoniazid, lithium, streptomycin, sildenafil, and tobacco)

- Nutritional amblyopia (pernicious anemia, malabsorption syndrome)
- Hereditary optic neuropathy (Leber's)
- Neurosyphilis
- Choroidal melanoma
- Homocystinuria.

## INVESTIGATIONS—GENERAL

### CBC

- Severe anemia can cause retinal hemorrhage and exudates
- Increased hematocrit, WBC and platelet cell count in hypercoagulable states, e.g. retinal vascular occlusions.

### ESR

- Elevated in malignancy, temporal arteritis.

### Blood Glucose/HbA1C

- To monitor diabetes mellitus.

### Lipid Profile

- To evaluate hyperlipidemia, including serum homocysteine levels.

### Coagulation Screen

- PT, PPT, lupus anticoagulant, Factor V Leiden, antithrombin III, protein C, protein S, etc. are indicated in patients with hypercoagulable states, e.g. retinal vascular occlusions.

### TFTs

- In severe hyperthyroidism extraocular muscle entrapment (thyroid oculopathy) may cause progressive loss of visual acuity and visual field.

### IOP (Tonometry)

- Elevated in acute glaucoma; greater than 30 mm of Hg is highly suspicious.

\* In children common causes of visual failure are congenital cataract, retinitis pigmentosa and retinoblastoma.



**Visual Field (Perimetry)**

- Scotomas are common with glaucoma.
- Hemianopias, quadrantanopias in optic nerve lesions.

**INVESTIGATIONS—SPECIFIC****Fluorescein Angiography**

- In diabetic and hypertensive retinopathy, and retinal arterial/venous occlusion.

**US of Eye and Orbits**

- Helpful in detecting intraocular tumors, orbital tumors, retinal detachment, vitreous changes, thyroid oculopathy, and intraocular foreign bodies.

**CT Scan Skull, Orbits/MRI Brain**

- As indicated to diagnose tumor, multiple sclerosis.

**Carotid Doppler Scan**

- To assess carotid/vertebral circulation, and stenosis in CVD and TIA.

**Echocardiogram**

- To exclude embolic source in valvular heart disease, subacute bacterial endocarditis, and atrial myxoma.

**Visual Evoked Response (VER)**

- Most useful in the diagnosis of retinitis pigmentosa, optic nerve disease, and occasionally in demyelinating disorders, e.g. multiple sclerosis.

**Temporal Artery Biopsy**

- In patients with temporal (giant cell/cranial) arteritis.

**CLINICAL NOTES**

- Patients may not mention an eye complaint during initial discussion; however, a proactive approach (i.e. direct questions) to uncover any serious eye condition needs to be adopted during consultation, especially in the elderly with comorbid diseases such as diabetes and hypertension. Few simple questions, e.g. — ‘are you able to read newsprint or see TV; are your glasses adequate; are you being treated for any eye disease; when you last consulted your ophthalmologist’ — will alert the physician of an underlying disorder.
- The symptom of vision loss should be investigated further by asking following questions:
  - Onset—sudden, gradual or progressive
  - Unilateral or bilateral eye involvement
  - Is the vision impaired all the time (cataract, ARMD) or only at nights (retinitis pigmentosa)
  - Is the vision impaired only in part of visual field? e.g.—can the patient see objects directly in front of him but not those to the left and right without moving his head? This distinction between central and peripheral visual loss is useful. *Central visual loss* implies defective retinal vision formation, e.g. macular disease, optic neuropathy. *Peripheral visual loss* is more subtle, especially when the onset is gradual, and implies extramacular retinal disease or a defect in the visual pathway, e.g. hemianopia.
- Associated symptoms:
  - Pain on eye movements—common in optic neuritis, frequently precedes the onset of visual loss;
  - Flashing lights with eye movements and floaters, i.e. photopsia—common in retinal detachment

- Colored halos around lights, i.e. whenever patient looks at white light, he sees it as if white light is split into its component colors, red being outermost, seen in prodromal stage of angle closure glaucoma, and cataract.
- Current medications:<sup>4</sup> Systemically administered drugs produce a wide variety of adverse effects on the visual system; e.g. amiodarone, ethambutol, linezolid, sildenafil, long-term use of glucocorticoids, phenothiazine, adrenergic agents, certain  $\beta$ 2-adrenergic agonists, and anticholinergic agents.
- Associated disorders, e.g. tuberculosis, diabetes mellitus, hypertension, hyperlipidemia, thyroid disease, autoimmune disease, and malignancy.
- Past history of ocular disease or surgery, e.g. orbital trauma, FB, corneal ulcer.
- Family history, e.g. developmental cataracts, corneal dystrophies, retinitis pigmentosa, Leber's hereditary neuropathy.
- Physical examination includes tests for—
  - Visual acuity for distance and near, with and without glasses (Snellen chart) in all instances (except in chemical trauma<sup>†</sup>).
  - Visual field: (Table 48.2).
  - Analysis of central visual field with an *Amsler grid* (to locate macular blind spots and areas of distortion and wavy lines) used in daily self-monitoring for the progression of macular degeneration.
  - Pupillary reaction: (ref. swinging flashlight test, chapter 49: Vision Loss Sudden.)
  - Fundus examination (ophthalmoscope) with dilated pupil to assess the red reflex, optic disk for papilledema, and retina for presence of hemorrhage, cotton wool spots.

<sup>†</sup> In chemical exposure, the dictum is '*treat first, examine later*'; copious irrigation should be initiated before attempting a visual acuity examination.

**Table 48.2:** Visual field defects with localization of lesion

<i>Vision defect</i>	<i>Localization/examples</i>
Tunnel vision	Concentric diminution of field, e.g. glaucoma, late papilledema.
Enlarged blind spot	Early papilledema (optic nerve head enlargement)
Central scotoma, i.e. loss of central macular vision	Optic nerve head to chiasmal lesion, e.g. demyelination, vascular, toxic, nutritional.
Unilateral field loss, i.e. monocular field defect	Optic nerve lesion, e.g. tumor, vascular.
Bitemporal hemianopia	Optic chiasma lesion, e.g. pituitary tumor
Hemonymous hemianopia	Lesion behind optic chiasma, i.e. optic tract to occipital cortex
Upper quadrant homonymous hemianopia	Optic radiation (Temporal), e.g. tumor, vascular
Lower quadrant homonymous hemianopia	Optic radiation (Parietal)
Homonymous hemianopia with central vision (macula) sparing	Occipital cortex

- Systemic examination for any collaborative evidence for loss of vision is important. For example:
  - Stenotic vascular disease (carotid or vertebral artery atherosclerotic disease, arteritis, dissection)
  - Cardiac disease (hypertension, endocarditis, atrial myxoma, valvular disorders)
  - Autoimmune disease (RA, ankylosing spondylitis, giant cell arthritis, SLE)
  - Granulomatous disease (sarcoidosis)
  - Hematological (anemia, hypercoagulable states, antiphospholipid syndrome)
  - Neurological (head injury, mass lesion, seizures, MS)
  - Psychological (conversion syndromes, malingering).

## RED FLAGS

- Documentation of the initial visual acuity and visual field, and their subsequent assessment can be important in a disability or malpractice lawsuit.
- The presence of a cataract in relatively young patient (e.g. juvenile diabetic cataract) is unusual and shall prompt ophthalmic consult.
- Gradual vision loss associated with progressive early morning headache is an indication of intracranial neoplasm; urgent referral is indicated.
- Prompt ophthalmic referral is prudent in all intraocular hemorrhages, including subcon-

junctival bleeding, which can be ominous, e.g. in patients with bleeding dyscrasias.

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## CHAPTER

# 49

## Vision Loss—Sudden

### SYNOPSIS

Sudden vision loss (SVL) or acute visual loss is an ophthalmic emergency requiring *immediate* medical attention to avert permanent visual impairment.

SVL means anything from instantaneously to over the course of a week (Table 49.1). It can be total, partial, transient, or permanent; involving either one or both the eyes.

Patients with SVL present with variable symptoms. Some patients describe it as a gray-black curtain that moves up or down, fogging, blurring, dimming vision, halos around lights, flashing lights, and ‘spider webs’ in peripheral vision.

The physician’s role is to recognize the signs and symptoms of SVL, assess the vision rapidly, obtain an *immediate* ophthalmic consult, and stabilize the patient until the patient is seen by an ophthalmologist.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Acute angle closure glaucoma (AACG)
- Vitreous hemorrhage

**Table 49.1:** Time-scale development of visual loss

#### *Sudden: less than 1 hour*

- Amaurosis fugax
- Central retinal artery occlusion
- Acute angle closed glaucoma
- Vitreous hemorrhage
- Migraine

#### *Within 24 hours*

- Central retinal venous occlusion
- Hysteria

#### *Less than 7 days*

- Retinal detachment
- Optic neuritis
- Endophthalmitis (after injury or postoperative)

#### *Up to several weeks/months/gradual*

- Papilledema
- Malignant hypertension
- Cataracts
- Diabetic retinopathy
- Macular degeneration
- Chronic glaucoma
- Compression of visual pathway
- Retinitis pigmentosa

- Central retinal venous occlusion (CRVO)
- Cerebrovascular accidents
- Transient ischemic attack (anterior circulation)
- Migraine (ophthalmoplegic).

### Occasional

- Nonarteritic anterior ischemic optic neuropathy<sup>1</sup> (NAION: *vide infra* ↓↓)
- Arteritic anterior ischemic optic neuropathy (AAION,\* e.g. temporal arteritis)
- Central retinal artery occlusion (CRAO)
- Retinal detachment
- Posterior uveitis
- Cortical blindness.

### Rare

- Trauma (optic nerve injury, ruptured globe)
- Acute demyelinating optic neuritis<sup>2</sup> (multiple sclerosis)
- Malingering.

## INVESTIGATIONS—GENERAL AND SPECIFIC

(Ref. Chapter 48: Vision Loss – Gradual p. 330)

### CLINICAL NOTES

- Many causes of loss of vision (sudden and gradual) have a vascular etiology and generally affect older patients. In these cases it is important to search for and treat systemic hypertension, diabetes, cardiac, and carotid disease
- In addition to historical notes explained in the Chapter 48 'Vision Loss – Gradual', (p. 330), the following physical examination should be performed in rapid sequence
- As the patient's assessment of visual loss and its severity is highly subjective, a quick objective assessment of the vision should be done after testing each eye separately with a Snellen chart, whenever possible.

\* There are 2 types: arteritic and nonarteritic. AAION is an inflammatory vasculitis, and NAION is a diagnosis of exclusion, which is made in the absence of provable arteritis. NAION is more common than AAION due to temporal arteritis. NAION is the most common acute optic neuropathy and one of the most common causes of sudden vision loss in the elderly.

### Visual field:

- A quick assessment of the vision may be done, testing each eye separately.
- If possible, assess acuity using a Snellen chart at 3 meters instead of 6; if the patient sees the top letter (6/60), it would be recorded as 3/60.
- If the acuity is less than 3/60, check if the patient can count fingers (CF) at a distance of one meter, or see hand movements (HM).
- If he cannot CF or see HM, check if he can perceive a bright light (by shining the bright light in each eye), and note whether there is perception of light (PL) or not (no PL or NPL).
- Checking the confrontation fields, with HM in the four quadrants give an idea of visual field loss.
- Swinging flashlight test: (objective)
  - This test is performed to test for *relative afferent pupillary defect* (RAPD)<sup>†</sup>, also called as *Marcus Gunn pupil*.
  - The test is performed by having the patient look into the distance and then shining a light into one eye, thus eliciting pupillary constriction in that eye and consensual constriction in the other eye. The light is then quickly moved in front of the other pupil, which normally should constrict further. If this additional constriction does not occur and the pupil dilates instead, RAPD is present. The test is repeated several times. The presence of RAPD requires further evaluation by an ophthalmologist.
- Causes of SVL are generally grouped in two, namely, bilateral and unilateral, most of them either being transitory, and few causing permanent visual loss. (Tables 49.2 and 49.3).

<sup>†</sup> RAPD is always unilateral. Since light in one pupil causes both pupils to constrict, quickly switching from one eye to the other will give a "relative" indication of the functioning of each eye and optic nerve. If both eyes are equally dysfunctional, no "relative" defect would be found; hence 'bilateral' RAPD does not exist.

**Table 49.2:** Bilateral vision loss of sudden onset

- Migraine with usual aura
- Vertebral artery spasm/embolism
- Bilateral optic nerve damage
- Occipital lobe infarction
- Occipital lobe trauma

**Table 49.3:** Unilateral vision loss of sudden onset

- Amaurosis fugax
- Migraine with visual aura
- Central retinal artery/vein occlusion
- Acute angle closed glaucoma
- Retinal detachment
- Vitreous hemorrhage
- Temporal arteritis
- Optic neuritis (e.g. multiple sclerosis)
- Ischemic optic neuropathy

- Hysterical blindness or loss of vision—A purely functional loss of vision can be assumed when the orientation while walking is intact, pupillary light reflex is normal, and visual field is markedly restricted or inconsistent on repeated examination. If the patient indicates a unilateral loss of vision, the examination should be conducted in such a way that the patient is unaware of which eye is being tested or the actual size of the optotypes.

## RED FLAGS

- In an elderly with SVL—Exclude temporal arteritis that is typically associated with high ESR; timely high-dose steroids will avert permanent visual loss in the affected eye and protects the other eye from the same fate. This is one critical situation where a physician takes immediate precedence over an ophthalmologist
- Beware of atypical presentations, e.g. nausea, vomiting, or abdominal pain, and/or a seemingly innocuous red eye; AACG may be missed

- Due care must also be taken not to diagnose seemingly inappropriate behavior (due to vision loss) as of psychogenic in origin
- Beware of acute presentation of vision loss that is actually of chronic (gradual) onset, but suddenly noticed by the patient.

## SELECTIVE GLOSSARY

**Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)**<sup>3,4</sup>— It refers to an idiopathic ischemic process of the anterior portion of the optic nerve. The typical presentation is sudden and painless visual loss with examination features of an optic neuropathy. Among the various associated risk factors are optic disk morphology (crowded disk), advanced age, systemic arterial hypertension, diabetes mellitus, hyperlipidemia, nocturnal hypotension, hemoconcentration, hemodilution, and hypercoagulable states. Since the introduction of PDE-5 inhibitors for the management of erectile dysfunction 10 years ago, there have been a number of reports of patients developing, within hours of PDE-5 inhibitor use, permanent visual loss due to NAION. In some of the cases, visual loss recurred upon rechallenge with the drug. However, as the bulk of the evidence suggesting a relationship between PDE-5 inhibitor use and NAION comes from case reports and small series, it is difficult to ascertain if a cause-effect relationship truly exists. However, following a series of such case reports, WHO and FDA have labelled the association between use of PDE-5 inhibitors and risk of NAION as ‘possibly’ causal. NAION has also been reported in patients taking several other medications, specifically sumatriptan, amiodarone, and nasal decongestants.

Since NAION is not a disease entity but rather the common pathogenetic pathway of a large variety of diseases and conditions, and is often the result of several interacting factors, there is



no 'standard therapy' for NAION. Careful interdisciplinary work up in NAION frequently reveals previously unrecognized diseases requiring treatment according to internal medicine standards.

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## CHAPTER

# 50

## Weakness in the Arms and Legs

### SYNOPSIS

Weakness of the limbs is one of the most common complaints presented to the physician, which may be part of any debilitating illness such as systemic infection, malignancy, or psychiatric disorder. In such cases there are usually pointers to the cause of suspected disorder. But, when limb weakness, i.e. true lack of strength is the only principal complaint, it is more likely that there is an underlying neuromuscular disease.

Since weakness of neuromuscular origin is manifested by objective evidence of reduced muscular strength, physically testing the strength of an individual muscle or muscle group is an important early step in the evaluation of weakness.\* The following standardized physical findings are followed in grading muscle strength on the scale of 0 to 5 'out of five'.

Neuromuscular diseases that result in limb weakness are best understood on the basis of neuroanatomy of the motor pathways, which consists of four integrated systems:

- 1 – The upper motor neuron (UMN) system
- 2 – The lower motor neuron (LMN) system

\* Muscle must be tested in such a way that the examiner's and the patient's strength are fairly evenly matched.

Grade	Muscle examination
0/5	No muscle movement (i.e. complete paralysis)
1/5	Variable muscle movement (i.e. flicker of contraction possible), but no movement at the joint
2/5	Movement is possible at the joint, but not against gravity
3/5	Movement against gravity possible, but not against added resistance
4/5	Movement against resistance possible, but less than normal
5/5	Normal strength

- 3 – The neuromuscular junction transmission system
- 4 – The skeletal muscle

Normal muscle strength depends principally on normal functioning of a relay of the above four systems, and any dysfunction at one or more of these four levels, which includes malfunction in the cerebral hemisphere, brainstem, spinal cord, nerve roots, peripheral nerves, myoneural junctions, and within the muscle itself can manifest in neuromuscular diseases.

### DIFFERENTIAL DIAGNOSIS

#### Common

- Cerebrovascular disease (stroke):

TIA; cerebral infarction/thrombosis/embolism; Intracranial hemorrhage: subarachnoid hemorrhage/Subdural hematoma

- Trauma:  
Head injury; spinal cord injury: Vertebral displacement, fracture
- Infections:  
Bacterial — Meningitis, TB; tuberculoma.  
Viral — Meningitis, encephalitis, herpes, and HIV  
Cerebral abscess  
Spinal epidural abscess
- Peripheral neuropathies:  
Diabetes mellitus  
Alcoholism  
Nutritional deficiencies—thiamine, vit.B<sub>12</sub>, folic acid
- Cervical and lumbar radiculopathies:  
Cervical spondylotic myelopathy  
Lumbar disc. herniation.

### Occasional

- Hypertensive encephalopathy
- Trauma (chronic subdural hematoma)
- Infections:  
Protozoal (malaria, toxoplasmosis)  
Helmenthic (cysticercosis, hydatid disease)  
Fungal (cryptococcus, *Candida*)
- Intracranial neoplasm (glioma, meningioma)
- Spinal cord neoplasm (both intramedullary and extramedullary)
- Metastases (cerebral and spinal: from breast, bronchus, prostate)
- Inflammatory (Guillain Barré syndrome, i.e. GBS)
- HIV associated myelopathy
- Entrapment neuropathies:  
Brachial plexus lesion (Erb-Duchenne)  
Ulnar nerve palsy (claw hand)  
Radial nerve palsy (wrist drop, Saturday night palsy)  
Median nerve palsy (carpal tunnel syndrome)  
Peroneal palsy (foot drop)

- Spinal cord infarction (cerebral spinal artery thrombosis).

### Rare

- Cerebral venous sinus thrombosis:  
Cavernous sinus thrombosis  
Superior sagittal vein thrombosis
- Multiple sclerosis or other demyelinating disorder
- Motor neuron disease:  
Progressive muscular atrophy  
Amyotrophic lateral sclerosis (ALS)  
Progressive bulbar palsy
- Muscular dystrophy
- Neuromuscular junction disease (Myasthenia gravis)
- Spinal cord disease (syringomyelia, syringobulbia)
- Metabolic (acute porphyria)
- Infections (poliomyelitis, tetanus, rabies, syphilis).

## INVESTIGATIONS—GENERAL

### CBC

- Hb may be reduced in chronic infection / inflammation; exacerbates muscular weakness.
- Pernicious anemia is common in nutritional deficiency causing weakness.

### ESR

- Elevated in infection, inflammation, autoimmune disorders.

### Blood Glucose

- To monitor hypoglycemia and hyperglycemia associated with weakness, neuropathy.

### Biochemistry and Metabolic Panel

- LFT, urea, electrolytes, calcium – to evaluate associated disorders.

### Thyroid Function Tests

- Hypothyroid and thyrotoxicosis can cause muscular weakness
- Myasthenia gravis (thymic tumor) may be associated with thyrotoxicosis.

### CT Scan Brain

- Ideally it should be done on every patient with stroke *as soon as possible*. If the deficit is secondary to hemorrhage, it will immediately be apparent (and such patients should not be anticoagulated)
- It is important to correlate CT scan findings with patient's neurologic examination; patients with old or clinically silent infarcts may be irrelevant to the acute situation.

### X-ray Skull, Cervical and Lumbosacral Spine

- To evaluate fracture of skull vault or base
- Spinal X-rays for fracture, infection, inflammation, degenerative, and metastatic lesions.

### CXR

- May show lytic bone or mass lesion due to bronchial cancer
- Lateral and anteroposterior view of CXR may demonstrate thymoma.

## INVESTIGATIONS—SPECIFIC

### Blood Culture

- For specific bacterial, viral, fungal organisms causing meningitis, encephalitis.

### Creatine Kinase (Total)—(CK)

- Markedly elevated, 10 to 200 times normal, in muscular dystrophy, and inflammatory myopathies

- Elevated, 2 to 3 times normal in MND.

### Serum Acetylcholine Receptor Antibody Titer

- Elevated levels in myasthenia gravis.

### ANA

- In rheumatologic myopathy: If ANA is positive, additional work up may include rheumatoid factor (rheumatoid arthritis), antidouble-stranded DNA or antiphospholipid antibodies (lupus), or anticentromere antibodies (scleroderma).

### Tensilon (Edrophonium chloride) Test

- In myasthenic patients, IV administration of edrophonium, there is an obvious improvement in strength of weak muscles lasting for about 5 minutes.

### Urine

- Estimation of urinary aminolaevulinic acid, porphobilinogen, and porphyrin in patients with porphyria.

### CT—Thorax

- CT of the anterior mediastinum may be indicated in patients suspected with thymoma (neoplastic change) in myasthenic patients with associated disorders
- A thymic shadow on CT scan may normally be present through young adulthood, but enlargement of the thymus in a patient > 40 years old is highly suspicious of thymoma.<sup>1, 2</sup>

### MRI—Cervical and Lumbosacral Spine

- Useful in obtaining more information about lesions already seen on CT scans and in diagnosing white matter lesions, e.g. multiple sclerosis, and lesions in the posterior fossa.

### Magnetic Resonance Angiography (MRA)

- Indicated to investigate abnormalities of intracerebral vessels such as arterial (berry) aneurysms or arteriovenous malformations, or to delineate blood supply of tumors prior to surgery.

### US (Duplex Scanning) of Carotid and Vertebral Arteries in the Neck

- Used as a screening tool to obtain information about the degree of respective arterial stenosis in patients with stroke.

### CSF Analysis

- Immediate lumbar puncture is indicated in suspected cases of CNS infection (without evidence of increased intracranial pressure)
- When a CT scan is not available and anticoagulants are anticipated; bloody or xanthochromic CSF should be a contraindication to anticoagulation
- Gram's stain of CSF sediment will show organisms in majority of untreated bacterial meningitis cases. India ink preparation for cryptococcus and AFB stains for TB bacilli are usually positive
- CSF culture should include bacteria (aerobic and anaerobic), TB, brucella, fungi, and viruses
- CSF for cryptococcal capsular antigen should be done when fungal meningitis is suspected, especially in those who are immunocompromised
- CSF for syphilis serology, e.g. venereal disease research laboratory test (VDRL), fluorescent treponemal antibody absorption test (FTA-ABS)
- CSF IgG and measles antibody titers must be obtained if subacute sclerosing panencephalitis (SSPE) is suspected
- PCR amplification of viral gene sequence can be performed in patients suspected with viral encephalitis and myelitis

- CSF electrophoresis normally detects oligoclonal bands in multiple sclerosis.

### Nerve Conduction Study (NCS)

- In various neuropathies to assess damage to peripheral nerves, and to determine whether the lesion is focal, diffuse, axonal, or demyelinating.

### Electromyography (EMG)

- Used to investigate disorders of neuromuscular transmission such as myasthenia gravis and myopathic disorders such as muscular dystrophies.

### Muscle Biopsy

- Confirms that the weakness is due to a primary disorder of muscle and to distinguish between various muscle diseases. Using MRI to identify focal areas of muscle abnormality can increase the diagnostic yield from muscle biopsies.

## CLINICAL NOTES

- A thorough history is essential to distinguish between primary (i.e. intrinsic) muscle weakness from ambiguous terms such as fatigue and asthenia (Table 50.1).
- *Fatigue* is a subjective feeling of weakness characterized by an inability to perform a task after multiple repetitions; in contrast, a patient with primary muscle weakness is unable to perform the first repetition of task. *Asthenia* is a sense of exhaustion in the absence of muscle weakness\*.
- The next step is assessment and localization of muscle weakness which includes:<sup>3</sup>

\* Fatigue and asthenia can coexist with primary muscle weakness which may lead to delay in the diagnosis of muscle disease because weakness is misinterpreted as fatigue/asthenia; specific screening tools may be essential to differentiate them.

**Table 50.1:** Common causes of fatigue and athenia

- Anemia
- Anxiety
- Addiction—abuse-alcohol, narcotics
- Cardiac disease CHF
- Chronic fatigue syndrome
- Depression
- Dehydration and electrolyte disorders
- Deconditioning/sedentary lifestyle
- Drugs — adverse effects
- Diabetes
- Fibromyalgia
- Hypothyroidism
- Infection — chronic-TB, hepatitis, HIV
- Pain—chronic
- Pregnancy/postpartum
- Pulmonary – COPD
- Renal – ESRD
- Sleep disorders

## 1. Distribution:

- a few muscles
- a limb (monoparesis)
- both lower limbs (paraparesis)
- both limbs on one side (hemiparesis)
- all four limbs (quadriparesis).

## 2. Type of weakness:

- upper motor neuron lesion
- lower motor neuron lesion
- both UMN and LMN, or neither.

## 3. Evolution of weakness:

- sudden and improving
- gradually worsening over days or weeks
- evolving over months or years

The time course of the onset of weakness, i.e. (evolution) is usually helpful in determining the possible etiology.

- Generally the rate of onset of limb weakness may be divided into acute, subacute, and chronic
- *Acute* onset limb weakness is typical vascular events, affecting contralateral UMN pathways, resulting in either hemiparesis or hemiplegia
- Sudden onset weakness in all four limbs (tetraparesis) or in both legs (paraparesis) is seen with spinal cord infarction, usually due

to occlusion of anterior spinal artery (common in patients with aortic atherosclerosis, aortic aneurysm)

- *Subacute* onset weakness in the limbs, i.e. evolving over a few days or weeks, is usually seen in diseases such as meningitis, encephalitis, neoplasms, multiple sclerosis, myasthenia gravis, and dermatomyositis
- *Chronic* limb weakness, which evolve over weeks or months (some overlap with disorders mentioned above), include motor neuron disease, most neuropathies, and many genetic muscular diseases
- The combination of UMN and LMN signs in a patient is an important clue to the diagnosis of motor neuron disease, e.g. ALS
- The combination of distal muscle weakness and sensory loss is commonly due to peripheral neuropathy
- The combination of proximal muscle weakness without sensory loss is commonly due to myopathy
- History should be focused to elicit information that will provide clues to the cause of weakness: (Table 50.2)
  - Onset—to establish if acute or chronic
  - Alteration of consciousness, headache, visual disturbances
  - Gait—disturbances of equilibrium
  - What muscles are affected by the weakness? e.g. foot, lower leg, thigh, upper arm, lower arm, facial, or back
  - Are both sides of the body affected by weakness and is it symmetrical? This information helps determine which joints, muscles and /or nerves may be affected, e.g. peripheral muscle weakness due to peripheral neuropathy is symmetrical compared with individual nerve or nerve root disease which should be suspected if weakness is asymmetrical or confined to one limb



**Table 50.2 : Historical clues for neuromuscular weakness**

<i>Findings</i>	<i>Probable diagnosis</i>
Acute weakness with neurologic deficit(s)	Stroke; spinal cord injury
Intermittent neurologic deficit	TIA
Fever, coryza, headache	Viral meningitis, encephalitis
Fever, otitis, sinusitis	Bacterial meningitis, cerebral abscess
Risky sexual exposure, Urethral discharge	Gonococcal, syphilis, HIV
Symptoms of raised intracranial pressure	Mass lesion
Exercise-provoked weakness	Myasthenia gravis
Heat-induced symptoms (hot sun, hot shower, fever); double vision-blurring; multiple neurologic deficit, exacerbations and remissions	Multiple sclerosis
Neck / back pain with or without radiation	Cervical spondylosis, degenerative disk disease
Rash around eyelids, difficulty arising from a chair	Dermatomyositis, polymyositis
Positive medication history	Drug-induced myopathy (statins, steroids, anti-retrovirals)
Positive family history	Muscular dystrophy, autoimmune disorder

- If there is limb weakness, are the facial muscles also affected by weakness? — weakness of the muscles of the face associated with weakness of the limbs would suggest a diagnosis of cerebrovascular disease, a mass in the brain or spinal cord
- Aggravating factors — They help to determine the cause of muscle weakness, e.g. muscle power decreases with use in myasthenia gravis
- Recent viral infection — May suggest a viral illness itself as the cause of muscle weakness, e.g. influenza or Guillain-Barré syndrome (symptoms begin 7-10 days after the infective illness)
- History of trauma — It can determine possible cause of muscle weakness
- Exercise history — Muscle overuse may cause muscle weakness.
- Past medical history — Diabetes and chronic renal failure can cause peripheral neuropathy which may result in muscle weakness; diabetes, hypertension and high cholesterol are risk factors for cerebrovascular disease (stroke) which may result in muscle weakness; pernicious anemia may cause subacute combined degeneration of the cord and muscle weakness. History of TB, malignancy may suggest infection or mass lesion
- Dietary history — Vit. B<sub>12</sub> deficiency can cause peripheral neuropathy which may result in muscle weakness
- Medications — Some medications can cause peripheral neuropathy, e.g. amiodarone, phenytoin, nitrofurantoin; some medications may increase risk of thrombotic cerebrovascular disease (stroke), e.g. oral contraceptive pill, hormone replacement therapy; some medications can increase the risk of hemorrhagic stroke, e.g. warfarin
- Cigarette smoking — It is a major risk factor for cerebrovascular disease
- Alcohol history — It can be a cause of peripheral neuropathy
- Family history — Strokes, diabetes, high cholesterol, hypertension, hereditary motor and sensory neuropathy, Duchenne muscular dystrophy
- Physical examination includes:
  - Gait, neck stiffness
  - Glasgow coma scale, (GCS) i.e. level of consciousness
  - Blood pressure, palpation of all peripheral pulses including carotids for bruits; cardiac examination for arrhythmias, murmur
  - Optic fundi for papilledema, diabetes and hypertensive retinal lesions.

- Examination of motor system includes:
    - Observation for gait, involuntary movements, muscle symmetry (left to right and proximal vs. distal), atrophy, especially in shoulder, hands, thigh muscles.
    - Muscle strength, deep tendon reflexes including plantar response, clonus, fasciculations and coordination of upper and lower limbs.
    - Testing for range of movements in a variety of joints may be necessary.
  - Examination of sensory system includes – testing sensation of upper and lower limbs for pain, touch, temperature and vibration sensation. Examination of each nerve of the limb is important.
  - *Arm drift* or pyramidal drift of an upper limb: Rather subtle weakness may be detected by having the patient close the eyes and hold both arms, palm up, extended at the wrist and elbow. With a pyramidal (UMN) lesion, the affected limb drifts downwards and medially. The forearm tends to pronate and the fingers flex slightly. This sign is often first to occur, sometimes before weakness or reflex changes become obvious.
- must be excluded before a vascular or thromboembolic cause for stroke is considered.
- Acute spastic paraparesis, i.e. bilateral lower limb paresis with increased tone, such as in prolapsed disk, traumatic vertebral fracture/displacement, collapsed vertebra, etc. is a medical emergency.
  - Myasthenia gravis should be strongly suspected in any patient who reports excessive weakness at the end of the day. The complaints of weakness are often bizarre, interpreted frequently as psychiatric disorder, especially since routine neurologic examination is normal in most patients.
  - Beware of Pancoast tumor of the lung in a patient with upper limb weakness with painful neuropathy (due to neoplastic infiltration of the lower trunk of the brachial plexus), especially when Horner's syndrome is present.
  - Paraneoplastic neurologic syndromes must be considered in the diagnosis of unusual, progressive neuromuscular syndrome.
  - Rule out lesions of extrapyramidal tracts (e.g. Parkinsonism) or cerebellar pathways which may also present as weakness, but without objective evidence of decreased muscle strength.

## RED FLAGS

- The following diseases, though not a part of primary neurologic etiology, must be excluded in a patient with muscular disorder, which can otherwise cause significant morbidity and mortality: 1-Adrenal insufficiency; 2-Electrolyte imbalance: sodium, potassium, and magnesium; 3- Hypercalcemia; 4- Porphyrias; and 5- Rabies.
- Complicated migraine, postictal (Todd's) paralysis, hypoglycemia, cardiac arrhythmia

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## CHAPTER

# 51

## Weight Loss

### SYNOPSIS

Maintenance of body weight is determined by the balance of caloric intake, absorption, utilization, and metabolic rate which is regulated by an intricate network of neural and hormonal factors.

In a healthy individual, body weight is maintained at a stable 'set-point', which tends to peak in the fifth to sixth decades of life. Once weight has peaked, there is a relative stability, i.e. remaining stable until age 65 to 70. After the seventh decade the elderly subject tends to develop very small decrements in weight at a rate of 0.1 to 0.2 kg/year. Therefore, any unusual weight loss should not be dismissed as part of the aging process.

Whereas dieting, self-starvation, and eating disorders (i.e. anorexia nervosa and bulimia nervosa) explain most cases of *intentional weight loss* (IWL), *unintentional weight loss* (UWL) can be difficult to evaluate because of its nonspecific concept and myriad diagnostic possibilities. Some patients may be undisturbed by their weight loss, may welcome it, and may even mistakenly attribute it to their attempts to loose weight. However, when a marked fall in weight is the sole or dominant symptom, it may suggest an organic etiology. Therefore, routine determination of body

weight is an important strategy in any clinical practice.

Clinically, UWL is defined as loss of 5% or more of usual body weight\* over a period of 6 months, especially when progressive. It is also categorized as *significant* when the weight loss is: 5% in one month, 7.5% in three months, and 10% in six months.<sup>1</sup> A *severe* weight loss is defined as any loss higher than those percentages in the same time interval stated above. This magnitude of weight loss can occur in people of all ages, and usually involves underlying systemic disease, especially in the elderly, resulting in increased morbidity and mortality rates. Therefore, an organized work up is essential for accurate and timely diagnosis. In the majority, investigations based on symptoms and physical findings reveal the underlying cause; a specific cause is not identified in approximately 15 to 25% of patients. In such minority of undiagnosed patients, it is always worth reviewing the patient's history, and a period of watchful waiting is

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\* Ideal body weight can be estimated based on height. For men, 106 lb (48.2 kg) is allotted for the first 5 ft, then 6 lb (2.7 kg) is added for each inch above 5 ft; for women, 100 lb (45.5 kg) is given for the first 5 ft, with 5 lb (2.2 kg) added for each additional inch.

preferable to blind pursuit of additional diagnostic testing that may yield few useful data, if the results of these initial tests are normal.<sup>2</sup>

## DIFFERENTIAL DIAGNOSIS

### Common

- Infection (aggressive TB, occult abscess, giardiasis, HIV/AIDS)
- Psychiatric (depression, bipolar disorder, personality disorders)
- Diabetes mellitus (poorly controlled Type 1 and Type 2)
- Nonmalignant GI disorders (PUD, advanced liver disease)
- Malignancy (gastrointestinal, hepatobiliary, lungs, breast, genitourinary, ovarian, prostate, lymphomas)
- Chronic drug use (digoxin, metformin, opiates, cytotoxics)
- Food faddism (eating disorders: anorexia nervosa, bulimia, and Eating Disorder-Not Otherwise Specified, i.e. ED-NOS:<sup>3</sup> *vide infra* ↓↓)
- Substance abuse (alcoholism)
- Physiologic anorexia of aging (poor dentition, xerostomia, altered taste).

### Occasional

- Nonmalignant GI disorders (chronic pancreatitis, gastroparesis)
- Hyperthyroidism
- Organ failure (advanced CHF, COPD, hepatic, and renal disease)
- Social stressful events (economic hardship, isolation).

### Rare

- Substance misuse (diuretics, laxatives, cocaine, amphetamine)
- Nonmalignant GI disorders (IBD, malabsorption, celiac disease)

- Neurologic (dementia, Parkinson's disease, stroke)
- Metabolic (hypercalcemia, hypokalemia)
- Endocrine (Addison's disease).

## INVESTIGATIONS—GENERAL

### CBC

- Hb reduced in infection, malignancy
- Leukocytosis due to infection in HIV
- Elevated MCV in alcoholism
- Macrocytic anemia in malabsorption, food faddism, and IBD.

### ESR

- Elevated frequently in infection, malignancy.

### Urinalysis

- Glucose with diabetes mellitus; ketone bodies with DKA and malnutrition.
- Proteinuria, hematuria in renal disorders.

### Blood Glucose

- To detect and monitor diabetes mellitus
- Hypoglycemia in Addison's disease.

### HIV

- In patients with any sexual risk factor.

### Urea, Creatinine, Electrolytes

- Progressively increasing levels in renal failure
- Hyponatremia with hyperkalemia in Addison's disease.

### Tuberculin or PPD Test

- A positive reaction ( $\geq 10$  mm of induration) indicates TB infection; may be negative in patients with severe weight loss and AIDS.

**LFTs**

- Elevated bilirubin, and transaminases; usually associated with hypoproteinemia in hepatic failure.

**TFTs**

- Decreased TSH with increased FT4 in primary hyperthyroidism.

**Serum Calcium**

- Hypercalcemia in malignancy, myeloma, and Addison's disease.

**CXR**

- Often reveals infiltrates (e.g. tuberculosis, pneumocystic carinii pneumonia due to opportunistic infections), mass (neoplasm), lymphadenopathy (lymphoma, sarcoidosis), fibrosis, and cardiac failure.

**Stool**

- Ova and parasites; occult blood in colorectal carcinoma.
- Cryptosporidium (in AIDS) can be detected with modified acid-fast stain.

**INVESTIGATIONS—SPECIFIC****US Abdomen/ Pelvis**

- May be indicated to evaluate suspected abdominal masses (with guided needle aspiration and biopsy), e.g. abscesses, organomegaly, ascites, lymphadenopathy, and biliary-tract dilatation.
- Bilateral small, scarred echogenic kidneys (<10 cm) suggest chronic renal failure.

**Endoscopy**

- Gastroscopy or colonoscopy with cytologic brushings and biopsies of suspicious lesions

to detect esophageal (including Barrett's esophagus), gastric, or colonic malignancy, especially in elderly patients with chronic loss of weight

- Distal duodenal or proximal jejunum biopsy may help to identify the cause of malabsorption such as celiac disease
- Colonoscopy may be performed to screen for malignancy in patients with IBD.

**CT / MRI Abdomen**

- Valuable to identify distant metastasis and direct invasion of adjacent structures (usually preoperatively).

**Fecal Fat**

- The standard collection is for 72 hours, on a normal diet containing at least 100 g of fat daily. Excretion of more than 10 g of fat/day of fat is abnormal and warrants further evaluation for malabsorption.

**Antigliadin Antibodies**

- IgG or IgA antigliadin antibodies may be detected in patients with celiac disease.

**Other Screening Procedures**

- In women, mammography and cervical Pap smear; PSA in men aged  $\geq 50$  years and in specific patients with risk factors.
- Mesenteric duplex US: In elderly patients suspected with mesenteric ischemia.
- Morning (AM) cortisol / ACTH stimulation test or cosyntropin stimulation test: Low plasma cortisol (<3 mcg/dl) at 8AM is diagnostic, especially if accompanied by simultaneous elevation of the plasma ACTH level (usually >200 pg/ml) is diagnostic of Adrenal insufficiency.

## CLINICAL NOTES

- The initial approach to evaluating a patient with UWL is to verify that weight loss has occurred, and its duration. This can be done directly by verifying patient's records if available; or indirectly by noting physical evidence of weight loss such as a change in clothing size or as observed by a family member. Once weight loss is confirmed, special attention should be focused on the following:
- Diet—Its composition, including total calory intake per day<sup>†</sup>
- Food habits—Especially in young women; their attitude towards food intake and body image should be assessed. Disturbed body image may be a clue to the presence of an eating disorder
- Lifestyle factors—Exercise; tobacco and alcohol consumption; drug abuse; sexual behaviour are important and frequently lead to other concerns
- Medications—Prescribed (ACE-inhibitors, digoxin, NSAIDs, theophylline, metformin), and over-the-counter should be reviewed
- Psychosocial factors—A thorough evaluation of sources of stress, depression, or special situational problems is important. All elderly patients with weight loss should undergo screening for dementia and depression<sup>‡</sup> which may provide evidence of a mood or eating disorder
- Appetite—Weight loss in spite of increased appetite and intake suggests diabetes mellitus, thyrotoxicosis, or bulimia; whereas weight loss with normal or decreased appetite is usually due to other systemic disorders such as infection, organ failure, malignancy, and psychologic illness.

<sup>†</sup> Web site: [www.mna-elderly.com](http://www.mna-elderly.com); for Mini Nutritional Assessment tool.

<sup>‡</sup> Refer to Mini-Mental State Examination (MMSE) and Yesavage's Geriatric Depression Scale in standard textbooks.

- Symptoms and signs—The key topics to cover in the history should include the American Cancer Society's seven warning signs of cancer. Therefore, the review of systemic symptoms must include history of fever, cough, dyspnea, abdominal pain, dysphagia, dyspepsia, nausea, vomiting, change in bowel habits, melena, hematochezia, headache, and other neurologic symptoms. Common clinical findings associated with weight loss are given in Table 51.1.

**Table 51.1 : Weight loss - clinical correlation**

<i>Associated symptom and/or sign</i>	<i>Common causes</i>
Appetite—normal or increased	Diabetes mellitus, hyperthyroidism, bulimia, pheochromocytoma
Appetite—diminished, anorexia	Anorexia nervosa, medication effect, drug abuse, uremia, liver / cardiac failure, malabsorption
Fever	Infection—TB, HIV; collagen disease
Lymphadenopathy	Infection, leukemia, lymphoma, sarcoidosis
Thyromegaly	Hyperthyroidism
Thyroid nodule	Toxic adenoma
Abdominal mass	Hepatomegaly, splenomegaly, renal mass, pancreatic neoplasm
Abnormal rectal/pelvic findings	Prostate, cervical, uterine lesion
Hyperpigmentation, hypotension	Addison's disease
Abnormal CXR	TB, CHF, COPD, neoplasm
Anorexia, normal physical examination, normal CXR	Anorexia nervosa, uremia, substance abuse, malabsorption, occult malignancy (pancreatic)

## RED FLAGS

- A high index of suspicion is essential to diagnose eating disorders; patients can be very manipulative, critical, and secretive, and commonly lie about food intake



- Consider depression in most patients with weight loss. It may be the primary cause or may coexist with any secondary illness
- UWL, when accompanied with anorexia, may be the only sign of malignancy
- Occult malignancy must be regarded as the most common cause of weight loss in the absence of major symptoms and signs
- Continued weight loss should be monitored even if the initial evaluation is nondiagnostic
- Weight loss may be the initial presentation of diabetic ketoacidosis
- Beware of the potential for associated substance abuse.

### SELECTIVE GLOSSARY

**Eating Disorder-Not Otherwise Specified—ED-NOS**(DSM IV TR-307.50) is an emerging issues in *Eating Disorders*; this diagnosis is given to patients who have significant eating disorder symptoms, but do not meet the full criteria for

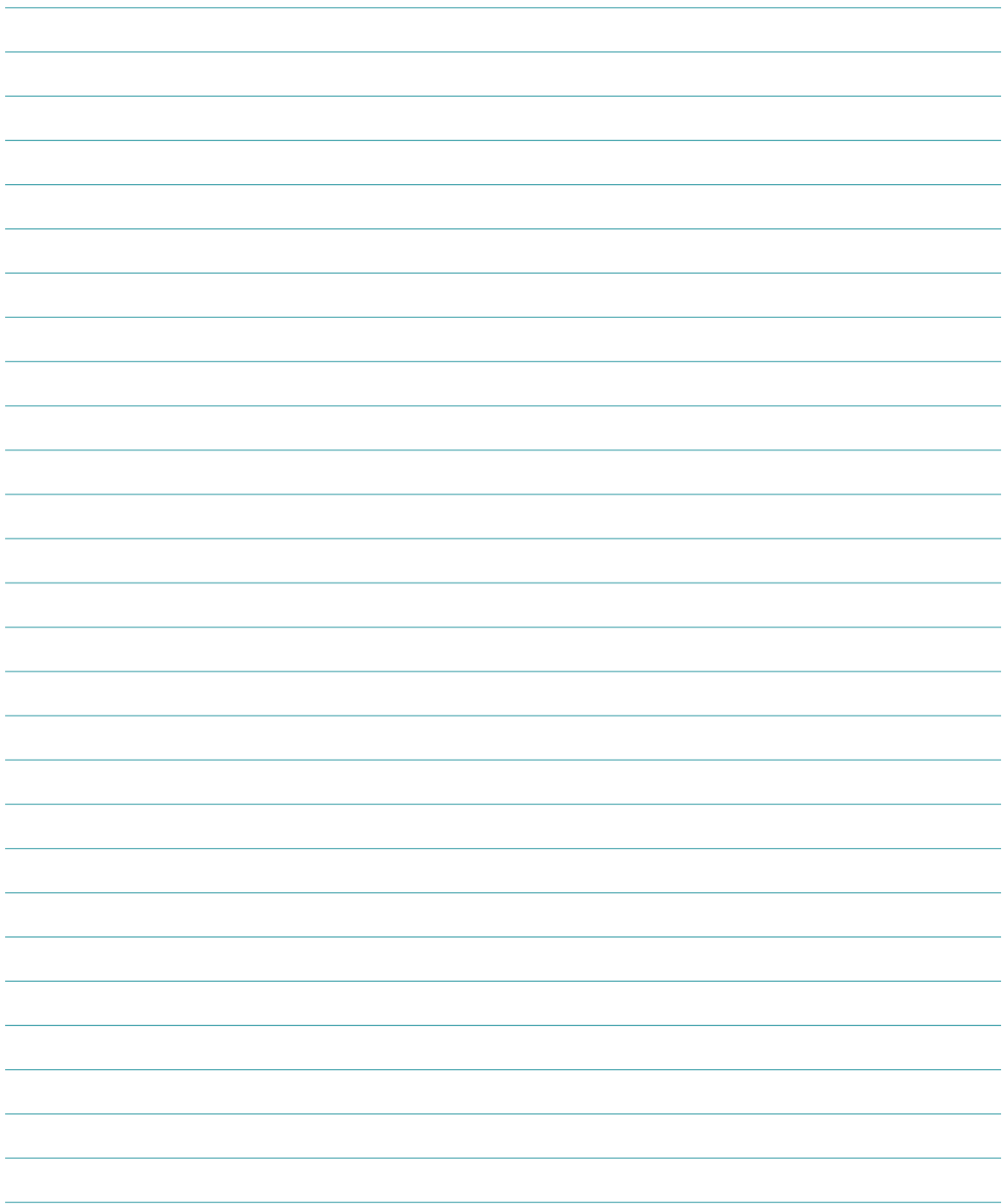
any specific eating disorder, and therefore present with subsyndromal cases of anorexia nervosa or bulimia nervosa. Examples include:

- A female of anorexia nervosa, except that she has regular menses
- A female of anorexia nervosa, without weight loss
- A female frequently indulging in self-induced vomiting after eating even a small food intake
- A female repeatedly chewing and spitting out, but not swallowing large amounts of food.

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